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(54) **MET-BINDING AGENTS AND USES THEREOF**

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(58) **Field of Classification Search**
None
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(57) **ABSTRACT**

The present invention relates to binding agents that specifically bind human MET, binding agents that specifically bind one or more components of the WNT pathway, bispecific agents that bind both human MET and one or more components of the WNT pathway, and methods of using the agents for treating diseases such as cancer.

21 Claims, 8 Drawing Sheets

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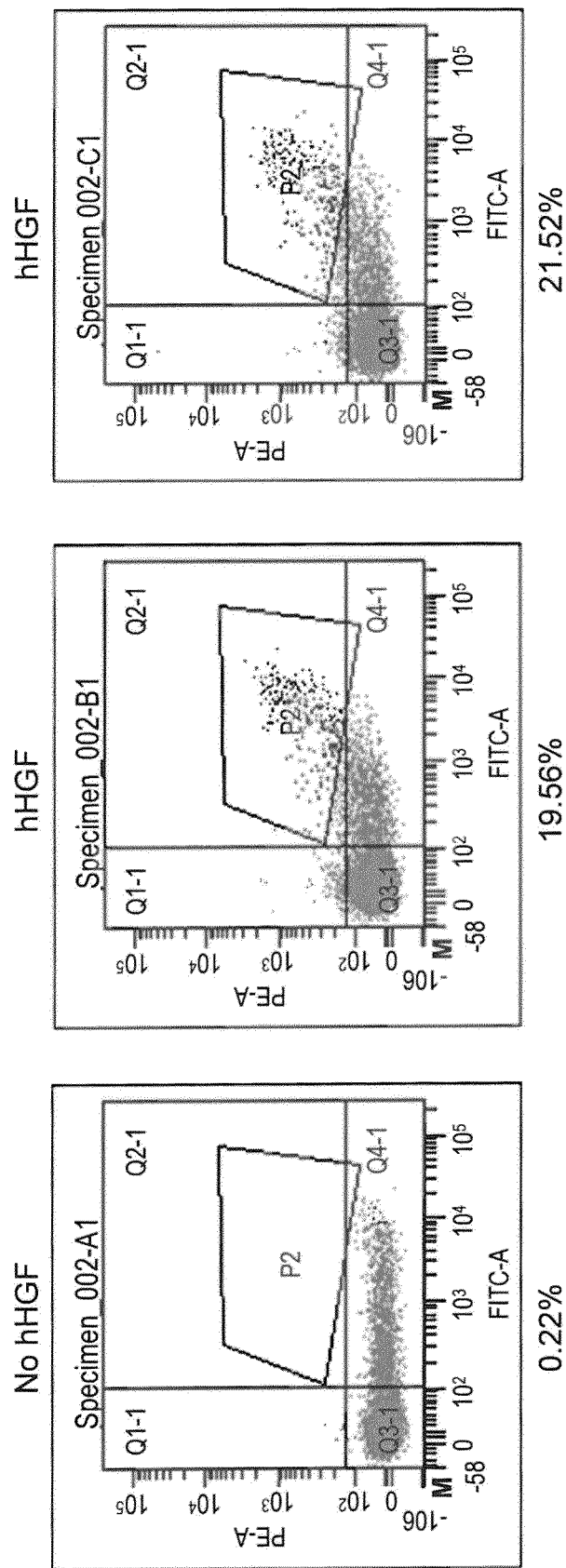
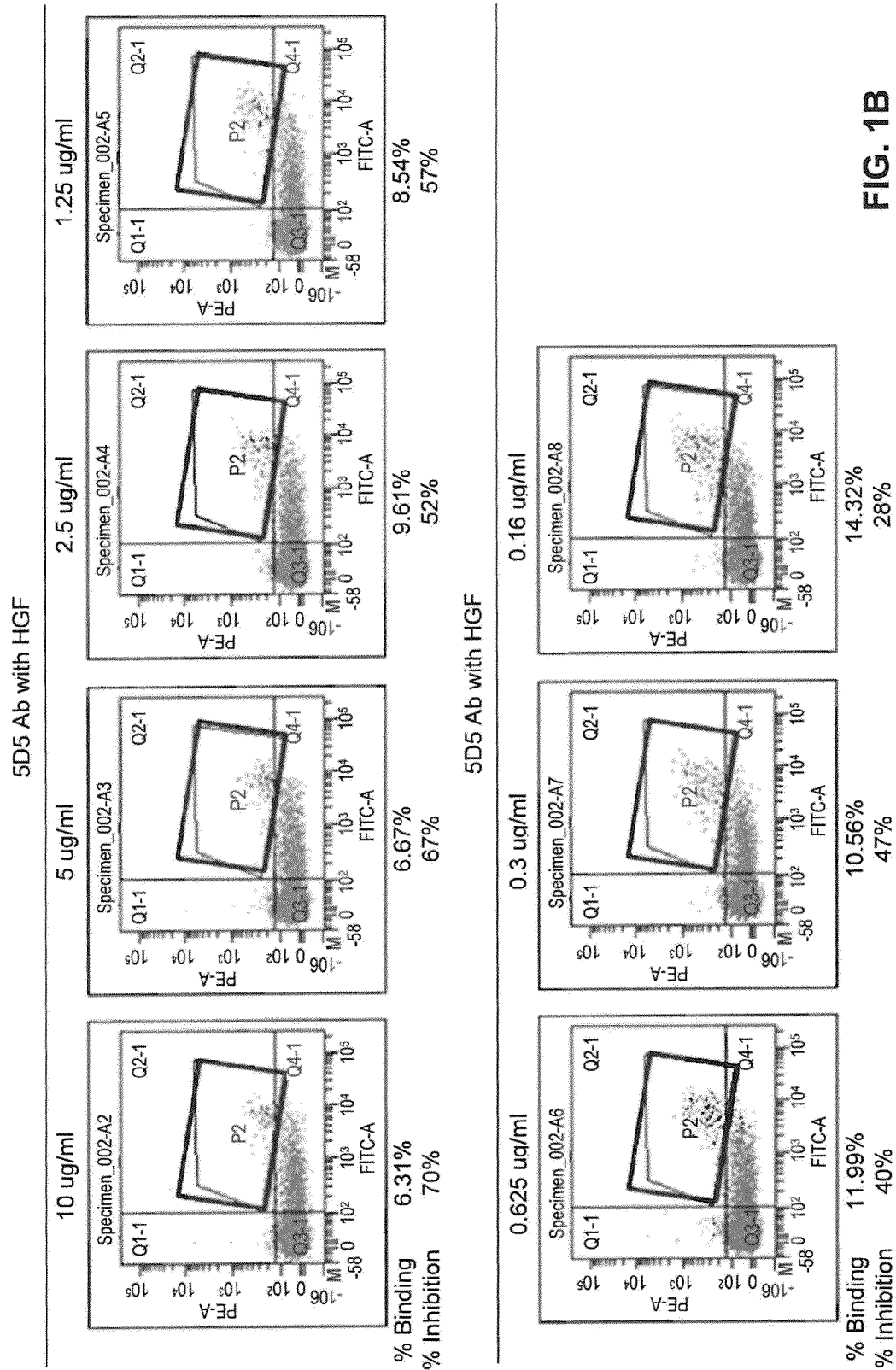


FIG. 1A



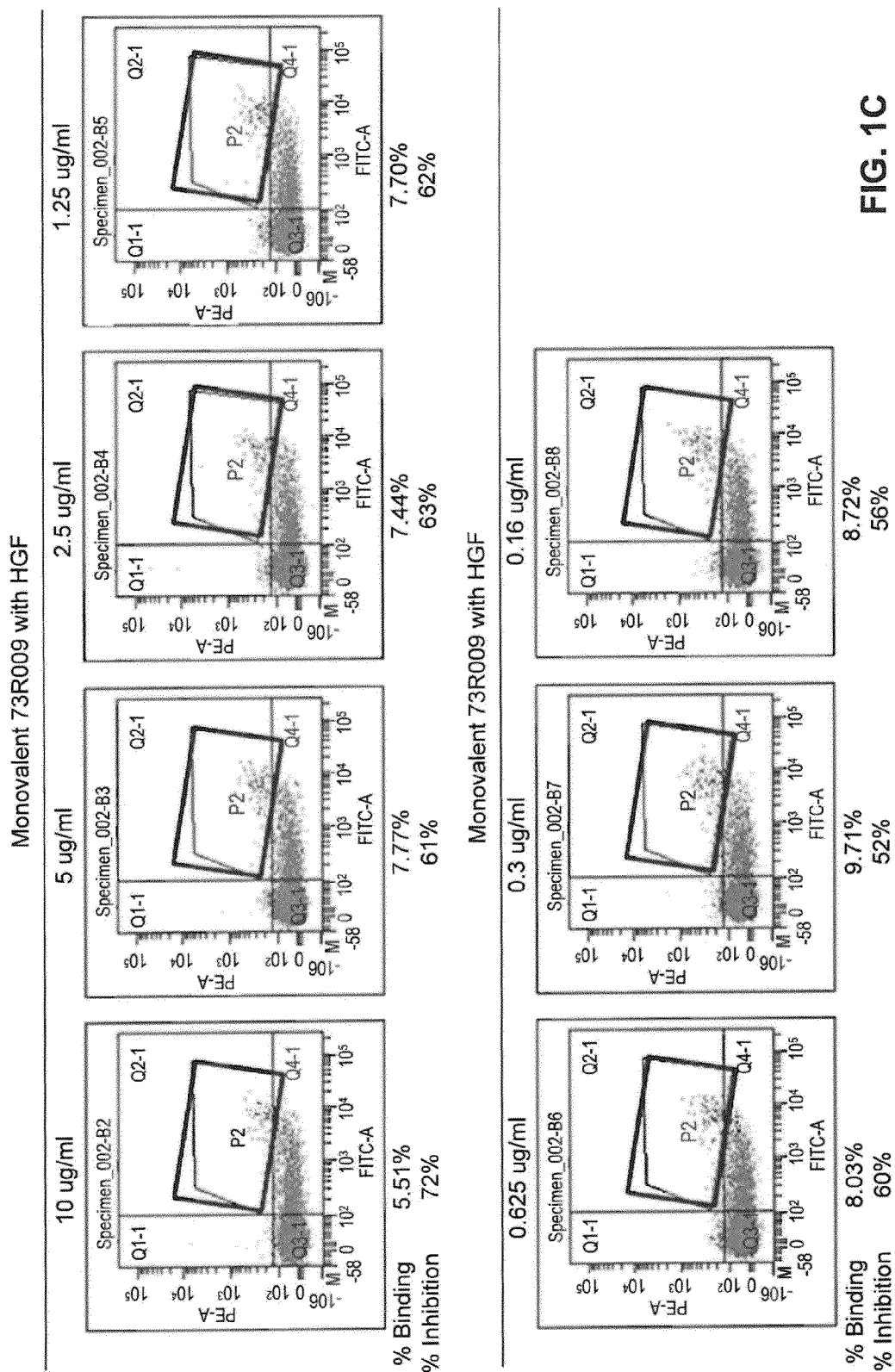


FIG. 1C

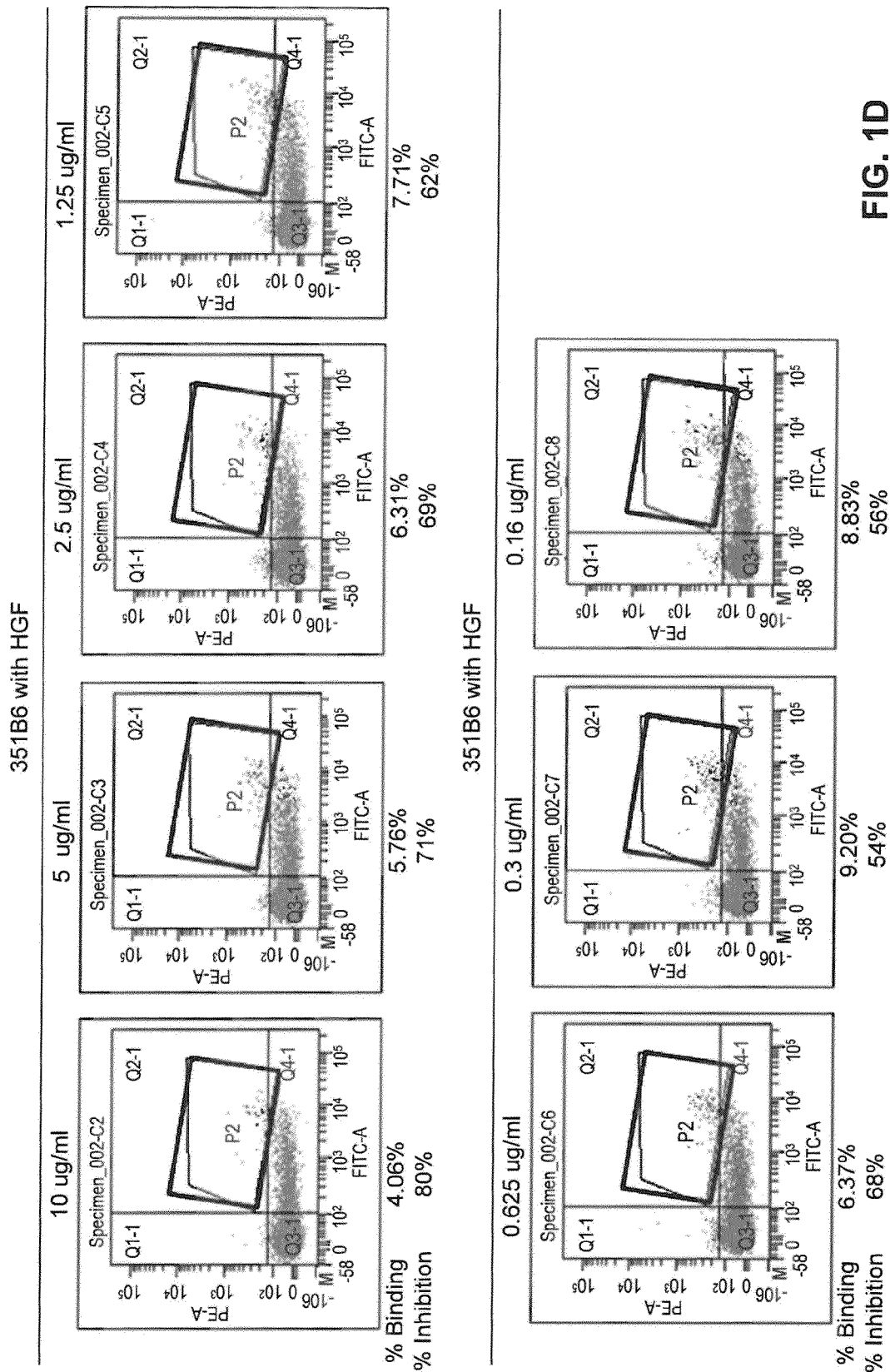


Figure 2

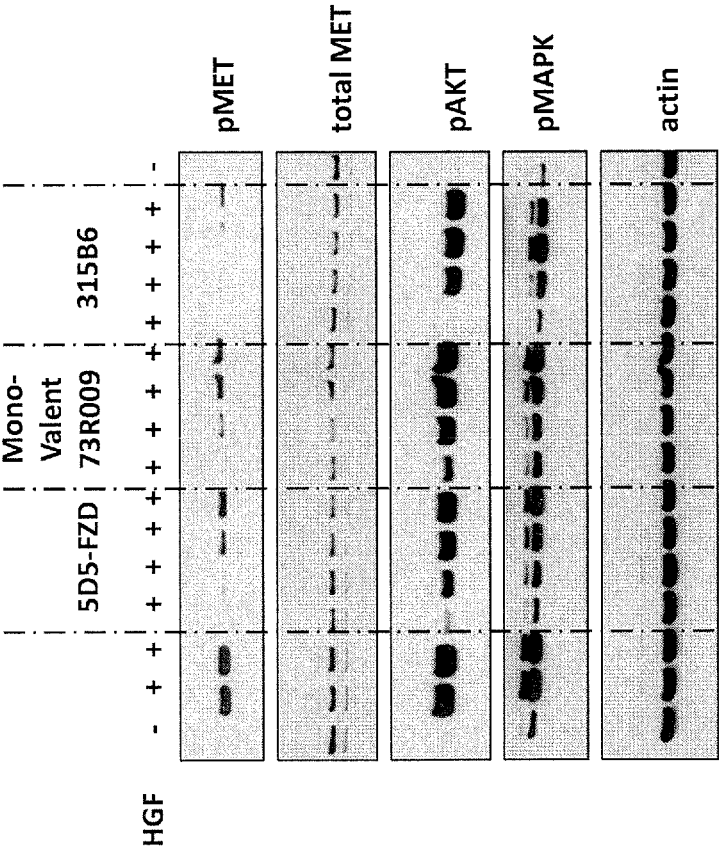
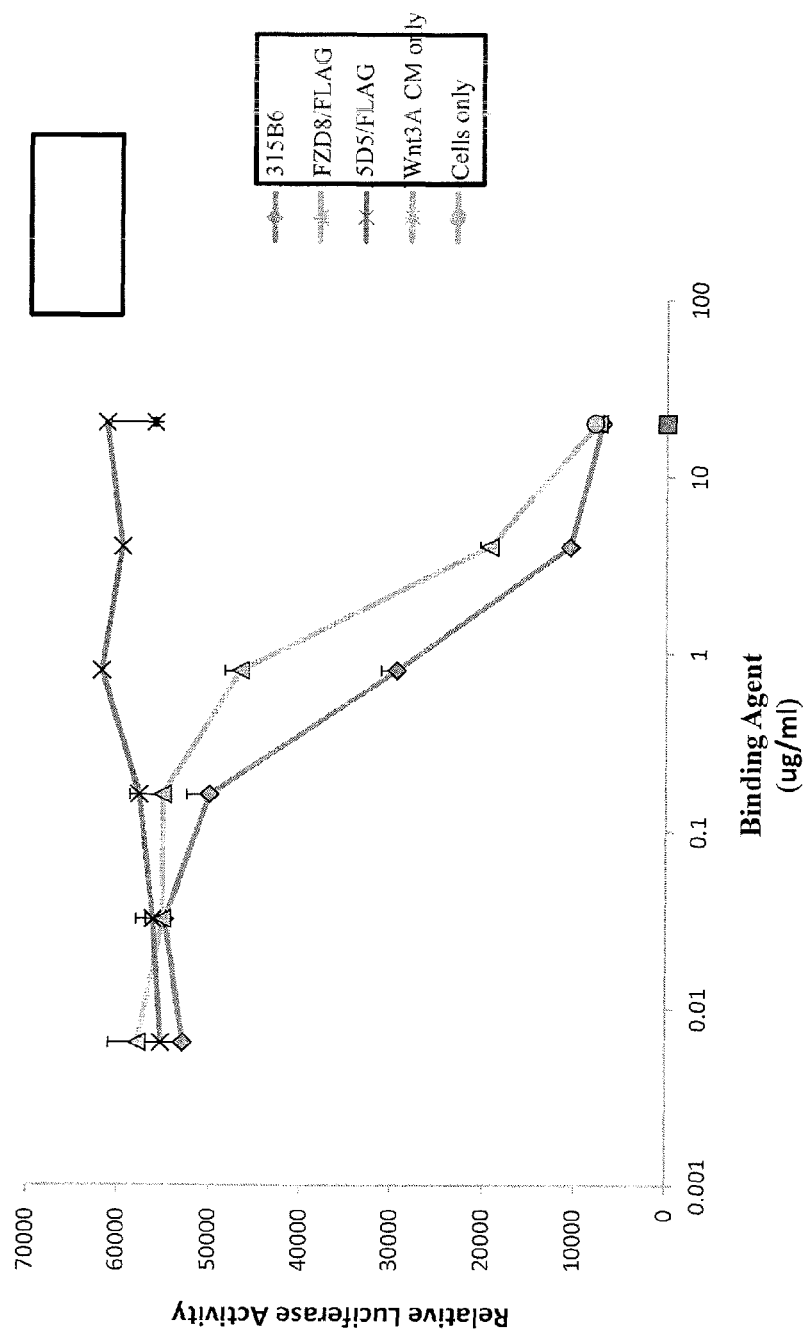


Figure 3



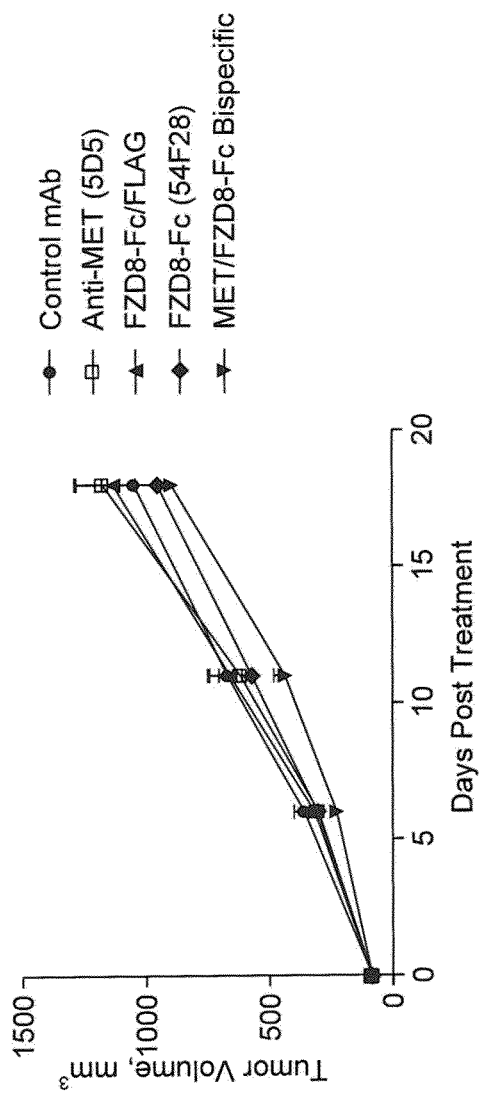


FIG. 4A

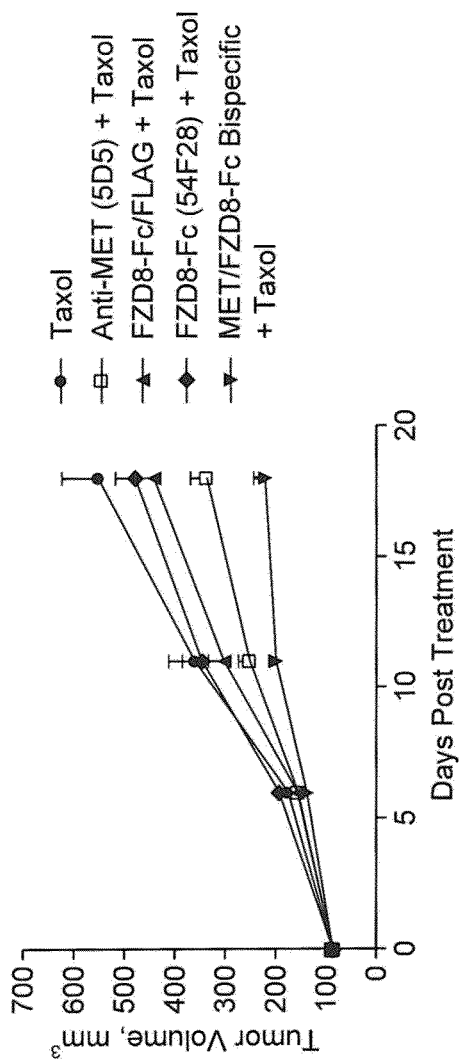


FIG. 4B

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MET-BINDING AGENTS AND USES THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority benefit of U.S. Provisional Application No. 61/783,552, filed Mar. 14, 2013, which is hereby incorporated by reference herein in its entirety.

REFERENCE TO A SEQUENCE LISTING SUBMITTED ELECTRONICALLY VIA EFS-WEB

The content of the electronically submitted sequence listing (Name: 22931070004SL.txt, Size: 144 kilobytes; and Date of Creation: Mar. 13, 2014) is herein incorporated by reference in its entirety.

FIELD OF THE INVENTION

The present invention generally relates to antibodies, bispecific agents, and other binding agents that bind MET, one or more components of the WNT pathway, or both MET and one or more components of the WNT pathway, particularly bispecific agents that bind both MET and one or more WNT proteins, as well as to methods of using the binding agents for the treatment of diseases such as cancer.

BACKGROUND OF THE INVENTION

Cancer is one of the leading causes of death in the developed world, with over one million people diagnosed with cancer and 500,000 deaths per year in the United States alone. Overall it is estimated that more than 1 in 3 people will develop some form of cancer during their lifetime. There are more than 200 different types of cancer, four of which—breast, lung, colorectal, and prostate—account for almost half of all new cases (Siegel et al., 2011, *CA: A Cancer J. Clin.* 61:212-236).

Signaling pathways normally connect extracellular signals to the nucleus leading to expression of genes that directly or indirectly control cell growth, differentiation, survival, and death. In a wide variety of cancers, signaling pathways are dysregulated and may be linked to tumor initiation and/or progression. Signaling pathways implicated in human oncogenesis include, but are not limited to, the WNT pathway, the Ras-Raf-MEK-ERK or MAPK pathway, the PI3K-AKT pathway, the MET/HGF pathway, the CDKN2A/CDK4 pathway, the Bcl-2/TP53 pathway, and the NOTCH pathway.

The MET/HGF (hepatocyte growth factor) pathway has been shown to play a critical role in early embryonic development. However, in adult tissues the MET pathway is tightly controlled and primarily quiescent in its growth signaling program, except in processes such as wound repair. Dysregulation of the MET pathway may lead to cell proliferation, protection from apoptosis, angiogenesis, invasion, and metastasis. MET may be dysregulated by a variety of different mechanisms including protein over-expression, constitutive activation, ligand-dependent activation, gene amplification, gene mutation, and/or MET modifications (e.g., phosphorylation). The MET pathway has been shown to be dysregulated in many tumor types, including but not limited to, lung, colorectal, breast, liver, gastric, pancreas, and brain.

The WNT signaling pathway is one of several critical regulators of embryonic pattern formation, post-embryonic tissue maintenance, and stem cell biology. More specifically, WNT signaling plays an important role in the generation of cell

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polarity and cell fate specification including self-renewal by stem cell populations. Unregulated activation of the WNT pathway is associated with numerous human cancers where it is believed the activation can alter the developmental fate of cells. The activation of the WNT pathway may maintain tumor cells in an undifferentiated state and/or lead to uncontrolled proliferation. Thus, carcinogenesis can proceed by overtaking homeostatic mechanisms that control normal development and tissue repair (reviewed in Reya & Clevers, 2005, *Nature*, 434:843-50; Beachy et al., 2004, *Nature*, 432:324-31).

The MET pathway and the WNT pathway have both been identified as potential targets for cancer therapy. It is one of the objectives of the present invention to provide improved molecules for cancer treatment, particularly bispecific agents that specifically bind human MET and one or more WNT proteins. Another objective of the invention is to use these novel bispecific agents to modulate the MET pathway and the WNT pathway and inhibit tumor growth.

SUMMARY OF THE INVENTION

The present invention provides binding agents, such as antibodies, soluble receptors, or bispecific agents that bind MET, one or more components of the WNT pathway, or both MET and one or more components of the WNT pathway, as well as compositions, such as pharmaceutical compositions, comprising the binding agents. Binding agents that bind MET, bind one or more components of the WNT pathway, or bind both MET and one or more components of the WNT pathway, and pharmaceutical compositions of such binding agents, are also provided. In certain embodiments, the binding agents are novel polypeptides, such as antibodies, antibody fragments, and other polypeptides related to such antibodies. In certain embodiments, the binding agents are novel polypeptides, such as soluble receptors and other polypeptides related to such soluble receptors. In certain embodiments, the binding agents are antibodies that specifically bind human MET. In some embodiments, the binding agents are antibodies that specifically bind one or more human WNT proteins. In some embodiments, the binding agents are antibodies that specifically bind one or more human Frizzled (FZD) proteins. In some embodiments, the binding agents are soluble FZD receptors that specifically bind one or more human WNT proteins. In some embodiments, the binding agents are bispecific agents that specifically bind human MET and one or more components of the WNT pathway. In some embodiments, the binding agents are bispecific agents that specifically bind human MET and one or more human WNT proteins. In some embodiments, the binding agents are bispecific molecules that specifically bind human MET and one or more human FZD proteins. The invention further provides methods of inhibiting the growth of a tumor by administering the binding agents to a subject with a tumor. The invention further provides methods of treating cancer by administering the binding agents to a subject in need thereof. In some embodiments, the methods of treating cancer or inhibiting tumor growth comprise targeting cancer stem cells with the binding agents. In certain embodiments, the methods comprise reducing the frequency of cancer stem cells in a tumor, reducing the number of cancer stem cells in a tumor, reducing the tumorigenicity of a tumor, and/or reducing the tumorigenicity of a tumor by reducing the number or frequency of cancer stem cells in the tumor.

In one aspect, the invention provides a binding agent, such as an antibody, that specifically binds human MET. In some embodiments, the binding agent inhibits binding of MET to

hepatocyte growth factor. In certain embodiments, the binding agent (e.g., a bispecific agent) specifically binds one or more components of the human WNT pathway in addition to binding human MET. In certain embodiments, the binding agent (e.g., a bispecific agent) specifically binds one or more human FZD proteins in addition to binding human MET. In certain embodiments, the binding agent (e.g., a bispecific agent) specifically binds one or more human WNT proteins in addition to binding human MET.

In certain embodiments, the binding agent specifically binds the extracellular domain of human MET. In some embodiments, the binding agent specifically binds the Sema domain of human MET. In some embodiments, the binding agent specifically binds within the Sema domain of human MET. In some embodiments, the binding agent specifically binds within amino acids 25-932 of human MET (SEQ ID NO:93). In some embodiments, the binding agent specifically binds within amino acids 25-836 of human MET (SEQ ID NO:93). In some embodiments, the binding agent specifically binds within amino acids 25-515 of human MET (SEQ ID NO:93). In some embodiments, the binding agent specifically binds within amino acids 563-836 of human MET (SEQ ID NO:93).

In some embodiments, the binding agent is an antibody that specifically binds human MET. In some embodiments, the MET-binding agent is an antibody that comprises a heavy chain CDR1 comprising ASYAWS (SEQ ID NO:1), a heavy chain CDR2 comprising YISYSGGTDYNPSLKS (SEQ ID NO:2), and a heavy chain CDR3 comprising KGAY (SEQ ID NO:3); and a light chain CDR1 comprising SASSSVSSSYLY (SEQ ID NO:4), a light chain CDR2 comprising STSNLAS (SEQ ID NO:5), and a light chain CDR3 comprising HQWSSYPYT (SEQ ID NO:6).

In certain embodiments, the MET-binding agent is an antibody that comprises a heavy chain variable region having at least about 80% sequence identity to SEQ ID NO:7; and/or a light chain variable region having at least about 80% sequence identity to SEQ ID NO:8. In certain embodiments, the binding agent comprises a heavy chain variable region having at least about 90% sequence identity to SEQ ID NO:7; and/or a light chain variable region having at least about 90% sequence identity to SEQ ID NO:8. In certain embodiments, the binding agent comprises a heavy chain variable region having at least about 95% sequence identity to SEQ ID NO:7; and/or a light chain variable region having at least about 95% sequence identity to SEQ ID NO:8. In certain embodiments, the binding agent is an antibody that comprises a heavy chain variable region of SEQ ID NO:7; and/or a light chain variable region of SEQ ID NO:8.

In some embodiments, the MET-binding agent is an antibody that comprises a heavy chain of SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:13, or SEQ ID NO:88; and/or a light chain of SEQ ID NO:11 or SEQ ID NO:14.

In some embodiments, the binding agent is antibody 73R009. In some embodiments, the binding agent is a variant of antibody 73R009. In some embodiments, the binding agent is a monovalent version of 73R009.

In another aspect, the invention provides a binding agent that is a bispecific agent, wherein the bispecific agent specifically binds human MET. In some embodiments, the bispecific agent specifically binds human MET and a second target. In some embodiments the bispecific agent binds human MET and one or more components of the human WNT pathway. In some embodiments, the bispecific agent binds both human MET and one or more human WNT proteins. In some embodiments, the bispecific agent is a bispecific antibody. In some embodiments, the bispecific antibody binds both

human MET and one or more components of the human WNT pathway. In some embodiments, the bispecific antibody binds both human MET and one or more human WNT proteins. In some embodiments, the bispecific antibody binds both human MET and one or more human FZD proteins. In certain embodiments, the bispecific antibody comprises two identical light chains. In certain embodiments the bispecific antibody is an IgG antibody. In certain embodiments the bispecific antibody is an IgG1 antibody. In certain embodiments the bispecific antibody is an IgG2 antibody.

In another aspect, the invention provides a bispecific agent that comprises a first arm that comprises a first binding site and a second arm that comprises a second binding site. In some embodiments, the first binding site comprises a first antigen-binding site from a first antibody and the second binding site comprises a second antibody-binding site from a second antibody. In some embodiments, the first binding site comprises an antigen-binding site from an antibody and the second binding site comprises a binding site that is not from an antibody. In some embodiments, the first arm comprises a monovalent antibody and the second arm comprises a soluble receptor.

In some embodiments, the bispecific agent comprises: a first binding site that specifically binds human MET, and a second binding site that specifically binds one or more components of the WNT pathway. In some embodiments, the bispecific agent comprises a first binding site that specifically binds human MET, and a second binding site that specifically binds one or more components of the WNT pathway, wherein the first binding site comprises a heavy chain CDR1 comprising ASYAWS (SEQ ID NO:1), a heavy chain CDR2 comprising YISYSGGTDYNPSLKS (SEQ ID NO:2), and a heavy chain CDR3 comprising KGAY (SEQ ID NO:3). In some embodiments, the bispecific agent further comprises: a light chain CDR1 comprising SASSSVSSSYLY (SEQ ID NO:4), a light chain CDR2 comprising STSNLAS (SEQ ID NO:5), and a light chain CDR3 comprising HQWSSYPYT (SEQ ID NO:6). In some embodiments, the bispecific agent comprises: a first binding site that specifically binds human MET, wherein the first binding site comprises (a) a heavy chain CDR1 comprising ASYAWS (SEQ ID NO:1), a heavy chain CDR2 comprising YISYSGGTDYNPSLKS (SEQ ID NO:2), and a heavy chain CDR3 comprising KGAY (SEQ ID NO:3), and a light chain CDR1 comprising SASSSVSSSYLY (SEQ ID NO:4), a light chain CDR2 comprising STSNLAS (SEQ ID NO:5), and a light chain CDR3 comprising HQWSSYPYT (SEQ ID NO:6).

In some embodiments, the bispecific agent comprises: a first binding site that specifically binds human MET, and a second binding site that specifically binds one or more components of the WNT pathway. In some embodiments, the bispecific agent comprises a first binding site that specifically binds human MET, and a second binding site that specifically binds one or more components of the WNT pathway, wherein the first binding site comprises a heavy chain CDR1 comprising GYTFTSYWLH (SEQ ID NO:78), a heavy chain CDR2 comprising GMIDPSNSDTRFNPFKD (SEQ ID NO:79), and a heavy chain CDR3 comprising TYGSYVSPLDY (SEQ ID NO:81), SYGSYVSPLDY (SEQ ID NO:82), ATYG-SYVSPLDY (SEQ ID NO:83), or XYGSYVSPLDY (SEQ ID NO:80), wherein X is not R; and a light chain CDR1 comprising KSSQSLLYTSSQKNYLA (SEQ ID NO:84), a light chain CDR2 comprising WASTRES (SEQ ID NO:85), and a light chain CDR3 comprising QQYYAYPWT (SEQ ID NO:86).

In some embodiments, the bispecific agent comprises a first binding site that specifically binds human MET, and a

second binding site that specifically binds one or more components of the WNT pathway, wherein the first binding site comprises a first antigen-binding site from a first antibody, and the second binding site comprises a second antigen-binding site from a second antibody. Thus, in some embodiments, the bispecific agent is a bispecific antibody. In some embodiments, the second binding site specifically binds one or more human WNT proteins. In some embodiments, the one or more WNT proteins is selected from the group consisting of: WNT1, WNT2, WNT2b, WNT3, WNT3a, WNT7a, WNT7b, WNT8a, WNT8b, WNT10a, and WNT10b. In some embodiments, the second binding site specifically binds one or more Frizzled (FZD) proteins. In some embodiments, the one or more FZD proteins is selected from the group consisting of: FZD1, FZD2, FZD3, FZD4, FZD5, FZD6, FZD7, FZD8, FZD9, and FZD10. In some embodiments, the one or more FZD proteins is selected from the group consisting of: FZD1, FZD2, FZD5, FZD7, and FZD8.

In some embodiments, the bispecific agent comprises a first binding site that specifically binds human MET, and a second binding site that specifically binds one or more components of the WNT pathway, wherein the second binding site comprises a soluble receptor. In some embodiments, the soluble receptor comprises an extracellular domain (ECD) of a human FZD protein. In some embodiments, the soluble receptor comprises a fragment of an ECD of a human FZD protein. In some embodiments, the soluble receptor comprises a Fri domain of a human FZD protein. In some embodiments, the soluble receptor comprises a Fri domain of a human FZD protein that comprises the Fri domain of FZD1, the Fri domain of FZD2, the Fri domain of FZD3, the Fri domain of FZD4, the Fri domain of FZD5, the Fri domain of FZD6, the Fri domain of FZD7, the Fri domain of FZD8, the Fri domain of FZD9, or the Fri domain of FZD10. In some embodiments, the soluble receptor comprises a Fri domain of a human FZD protein that comprises the Fri domain of FZD8. In some embodiments, the soluble receptor comprises a Fri domain of a human FZD protein that comprises a sequence selected from the group consisting of: SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, and SEQ ID NO:31. In some embodiments, the soluble receptor comprises a minimal core Fri domain of a human FZD protein that comprises a sequence selected from the group consisting of: SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, and SEQ ID NO:41. In some embodiments, the soluble receptor comprises a Fri domain of a human FZD protein of SEQ ID NO:28, SEQ ID NO:29, or SEQ ID NO:39. In some embodiments, the Fri domain of a human FZD protein is directly linked to a heterologous polypeptide. In some embodiments, the Fri domain of a human FZD protein is connected to a heterologous polypeptide by a linker. In some embodiments, the heterologous polypeptide comprises a human Fc region. In some embodiments, the heterologous polypeptide comprises: SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:91, or SEQ ID NO:92. In some embodiments, the soluble receptor comprises: (a) a first polypeptide of SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, or SEQ ID NO:41; and (b) a second polypeptide of SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:91, or SEQ ID NO:92, wherein the first polypeptide is connected to the second polypeptide by a linker. In some embodiments, the soluble receptor comprises a first polypeptide comprising SEQ ID NO:28. In some embodiments, the soluble receptor comprises a first polypeptide of SEQ ID NO:28. In some embodiments, the soluble receptor comprises a first polypeptide of SEQ ID NO:28, and a second polypeptide of SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, or SEQ ID NO:52. In some embodiments, the soluble receptor comprises a first polypeptide comprising SEQ ID NO:29. In some embodiments, the soluble receptor comprises a first polypeptide of SEQ ID NO:29. In some embodiments, the soluble receptor comprises a first polypeptide of SEQ ID NO:29, and a second polypeptide of SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, or SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, or SEQ ID NO:52. In some embodiments, the soluble receptor comprises SEQ ID NO:52 or SEQ ID NO:50. In some embodiments, the soluble receptor comprises SEQ ID NO:52.

SEQ ID NO:39, SEQ ID NO:40, or SEQ ID NO:41; and (b) a second polypeptide of SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:91, or SEQ ID NO:92, wherein the first polypeptide is directly linked to the second polypeptide. In some embodiments, the soluble receptor comprises: (a) a first polypeptide of SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, or SEQ ID NO:41; and (b) a second polypeptide of SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:91, or SEQ ID NO:92, wherein the first polypeptide is connected to the second polypeptide by a linker. In some embodiments, the soluble receptor comprises a first polypeptide comprising SEQ ID NO:28. In some embodiments, the soluble receptor comprises a first polypeptide of SEQ ID NO:28. In some embodiments, the soluble receptor comprises a first polypeptide of SEQ ID NO:28, and a second polypeptide of SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, or SEQ ID NO:52. In some embodiments, the soluble receptor comprises a first polypeptide comprising SEQ ID NO:29. In some embodiments, the soluble receptor comprises a first polypeptide of SEQ ID NO:29. In some embodiments, the soluble receptor comprises a first polypeptide of SEQ ID NO:29, and a second polypeptide of SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, or SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, or SEQ ID NO:52. In some embodiments, the soluble receptor comprises SEQ ID NO:52 or SEQ ID NO:50. In some embodiments, the soluble receptor comprises SEQ ID NO:52.

In some embodiments, the bispecific agent comprises a first arm that specifically binds human MET, and a second arm that specifically binds one or more components of the WNT pathway, wherein the first arm comprises a heavy chain CDR1 comprising ASYAWS (SEQ ID NO:1), a heavy chain CDR2 comprising YISYSGGTDYNPSLK (SEQ ID NO:2), and a heavy chain CDR3 comprising KGAY (SEQ ID NO:3), and a light chain CDR1 comprising SASSVSSSYLY (SEQ ID NO:4), a light chain CDR2 comprising STSNLAS (SEQ ID NO:5), and a light chain CDR3 comprising HQWSSYPYT (SEQ ID NO:6), and wherein the second arm comprises SEQ ID NO:56 or SEQ ID NO:87.

In some embodiments, a bispecific agent comprises a first binding site that specifically binds human MET, and a second binding site that specifically binds one or more components of the WNT pathway, wherein the first binding site comprises a heavy chain variable region having at least about 90% sequence identity to SEQ ID NO:7 and a light chain variable region having at least about 90% sequence identity to SEQ ID NO:8. In some embodiments, the first antigen-binding site comprises a heavy chain variable region having at least about 95% sequence identity to SEQ ID NO:7 and a light chain variable region have at least about 95% sequence identity to SEQ ID NO:8. In some embodiments, the first antigen-binding site comprises a heavy chain variable region of SEQ ID NO:7 and a light chain variable region of SEQ ID NO:8.

In some embodiments, a bispecific agent comprises a first arm that specifically binds human MET, and a second arm that specifically binds one or more components of the WNT pathway,

way, wherein the first arm comprises a heavy chain variable region having at least about 90% sequence identity to SEQ ID NO:7 and a light chain variable region having at least about 90% sequence identity to SEQ ID NO:8, and wherein the second arm comprises SEQ ID NO:56 or SEQ ID NO:87.

In some embodiments, the bispecific agent comprises (a) a first binding site that binds human MET with a K_D between about 0.1 nM and about 1.0 nM and (b) a second binding site that specifically binds one or more components of the human WNT pathway with a K_D between about 0.1 nM and about 20 nM.

In certain embodiments of each of the aforementioned aspects, as well as other aspects and/or embodiments described elsewhere herein, the binding agent is isolated. In certain embodiments of each of the aforementioned aspects, as well as other aspects and/or embodiments described elsewhere herein, the binding agent is substantially pure.

In another aspect, the invention provides a polypeptide selected from the group consisting of: SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:87, and SEQ ID NO:88. In some embodiments, the polypeptide is isolated. In certain embodiments, the polypeptide is substantially pure. In certain embodiments, the polypeptide is an antibody or part of an antibody, such as an antibody fragment. In some embodiments, the polypeptide is a soluble receptor or fragment of a soluble receptor. In some embodiments, the polypeptide is a fusion protein.

The invention further provides cells that comprise the bispecific agents, antibodies, or polypeptides described herein. The invention further provides cells that produce the bispecific agents, antibodies, or polypeptides described herein. In some embodiments, the cell is a prokaryotic cell. In some embodiments, the cell is an eukaryotic cell.

In another aspect, the invention provides isolated polynucleotide molecules comprising a polynucleotide that encodes the binding agents and/or polypeptides of each of the aforementioned aspects, as well as other aspects and/or embodiments described herein. In some embodiments, the polynucleotide comprises a polynucleotide sequence that encodes a sequence selected from the group consisting of: SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:87, and SEQ ID NO:88. In some embodiments, the polynucleotide comprises a sequence selected from the group consisting of: SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:89, and SEQ ID NO:90.

The invention further provides expression vectors that comprise the polynucleotides, as well as cells that comprise the expression vectors and/or the polynucleotides. In some embodiments, the cell is a prokaryotic cell. In some embodiments, the cell is an eukaryotic cell.

Pharmaceutical compositions comprising a binding agent, a bispecific agent, an antibody, or a polypeptide described herein and a pharmaceutically acceptable carrier are further provided.

In another aspect, the invention provides methods of using the binding agents, bispecific agents, antibodies, and/or polypeptides described herein. In some embodiments, a method of inhibiting growth of a tumor comprises contacting the tumor with an effective amount of a bispecific agent or antibody described herein. In some embodiments, a method of inhibiting growth of a tumor in a subject comprises administering to the subject a therapeutically effective amount of a

bispecific agent or antibody described herein. In some embodiments, a method of reducing the tumorigenicity of a tumor in a subject by reducing the frequency of cancer stem cells in the tumor comprises administering to the subject a therapeutically effective amount of a bispecific agent or antibody described herein. In some embodiments, a method of reducing the frequency of cancer stem cells in a tumor in a subject comprises administering to the subject a therapeutically effective amount of a bispecific agent or antibody described herein. In some embodiments, a method of inhibiting epithelial-mesenchymal transition (EMT) in a tumor in a subject comprises administering to the subject a therapeutically effective amount of a bispecific agent or antibody described herein. In some embodiments, the tumor is selected from the group consisting of colorectal tumor, colon tumor, ovarian tumor, pancreatic tumor, lung tumor, liver tumor, breast tumor, kidney tumor, prostate tumor, gastrointestinal tumor, melanoma, cervical tumor, bladder tumor, glioblastoma, and head and neck tumor.

In some embodiments, a method of treating cancer in a subject comprises administering to the subject a therapeutically effective amount of a bispecific agent or antibody described herein. The invention also provides a bispecific agent or antibody for use in a method of treating cancer, wherein the bispecific agent or antibody is an agent or antibody described herein. The invention also provides the use of a bispecific agent or antibody described herein for the manufacture of a medicament for the treatment of cancer. In some embodiments, the cancer is selected from the group consisting of colorectal cancer, colon cancer, ovarian cancer, pancreatic cancer, lung cancer, liver cancer, breast cancer, kidney cancer, prostate cancer, gastrointestinal cancer, melanoma, cervical cancer, bladder cancer, glioblastoma, and head and neck cancer. In some embodiments, a method further comprises administering at least one additional therapeutic agent.

The invention also provides a bispecific agent or antibody for use in a method of treating cancer, wherein the bispecific agent or antibody is an agent or antibody described herein. The invention also provides the use of a bispecific agent or antibody described herein for the manufacture of a medicament for the treatment of cancer.

Methods of treatment described herein comprising administering to a subject (e.g., a human) an effective amount of a binding agent, a bispecific agent, an antibody, or a polypeptide described herein as part of a pharmaceutical composition are also provided.

In another aspect, the invention provides a method of identifying a human subject or selecting a human subject for treatment with a binding agent, a bispecific agent, an antibody, or a polypeptide described herein. In some embodiments, the method comprises determining if the subject has a tumor that has an elevated expression level of MET as compared to a reference sample or a pre-determined level. In some embodiments, the method comprises identifying a subject for treatment or selecting a subject for treatment if the tumor has an elevated level of MET expression.

Where aspects or embodiments of the invention are described in terms of a Markush group or other grouping of alternatives, the present invention encompasses not only the entire group listed as a whole, but also each member of the group individually and all possible subgroups of the main group, and also the main group absent one or more of the group members. The present invention also envisages the explicit exclusion of one or more of any of the group members in the claimed invention.

BRIEF DESCRIPTIONS OF THE DRAWINGS

FIG. 1A-1D. Inhibition of binding of hepatocyte growth factor to human

MET. HEK-293T cells were transiently transfected with a human MET construct and then subsequently mixed with anti-MET antibody 5D5 (FIG. 1B), monovalent version of anti-MET antibody 73R009 (FIG. 1C), or anti-MET/FZD8-Fc bispecific agent 315B6 (Fig. 1D), and hepatocyte growth factor (HGF). Cells treated with only HGF were used as a positive control and untreated transfected cells were used as a negative control (FIG. 1A). Specific binding is indicated by the presence of signal within the box overlay on each FACS plot. The percent binding is shown underneath each FACS plot. The percent inhibition of binding as compared to the percent binding of the average of the two positive controls is shown underneath each FACS plot.

FIG. 2. Inhibition of MET activity induced by hepatocyte growth factor. A549 cells were pre-treated for one hour with monovalent version of anti-MET antibody 73R009, bispecific anti-MET/FZD8 agent 5D5/FZD8-Fc, or bispecific anti-MET/FZD8-Fc agent 315B6 and then stimulated with human hepatocyte growth factor. Cell lysates were analyzed by Western blotting.

FIG. 3. Inhibition of WNT signaling. A 8×TCF-luciferase reporter assay was used to measure WNT signaling in STF-293 cells. STF-293 cells were treated with anti-MET/FZD8-Fc bispecific agent 315B6 (—◆—) and control binding agents monovalent anti-MET antibody 5D5/FLAG (—X—) and monovalent FZD8-Fc FZD8/FLAG (—▲—). Cells were exposed to medium containing WNT3a L cell-conditioned medium or control medium from cells not over-expressing WNT3a (—●—).

FIG. 4A-4B. Inhibition of OMP-LU45 lung tumor growth. LU45 lung tumor cells were injected subcutaneously into NOD/SCID mice. Mice were treated with a control antibody (—●—), monovalent anti-MET antibody (5D5) (—□—), monovalent FZD8-Fc (—▲—), bivalent FZD8-Fc (54F28) (—◆—), anti-MET/FZD8-Fc bispecific (—▼—) without taxol (FIG. 4A) or in combination with taxol (FIG. 4B). Data is shown as tumor volume (mm³) over days post treatment.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides novel binding agents that bind MET, bind one or more components of the WNT pathway, or bind both MET and one or more components of the WNT pathway. The phrase “components of the WNT pathway” as used herein, generally refers to one or more WNT proteins and/or one or more FZD proteins. Related polypeptides and polynucleotides, compositions comprising the binding agents, and methods of making the binding agents are also provided. Methods of using the novel binding agents, such as methods of inhibiting tumor growth, methods of treating cancer, methods of reducing tumorigenicity of a tumor, methods of reducing the frequency of cancer stem cells in a tumor, methods of inhibiting EMT, methods of inhibiting angiogenesis, and/or methods of identifying and/or selecting subjects for treatment, are further provided.

A humanized monoclonal antibody that specifically binds human MET has been identified (73R009). This antibody has a binding affinity for human MET of about 1.1 nM and does not bind mouse MET. A monovalent version of the antibody has been generated and has a binding affinity for human MET of 1.4 nM. A bispecific agent that specifically binds human MET and one or more human WNT proteins has been produced, 315B6. Bispecific agent 315B6 has a binding affinity

for human MET of 1.8 nM and does not bind mouse MET. Bispecific agent 315B6 inhibits binding of human hepatocyte growth factor (HGF) to human MET (Example 2, FIG. 1). Bispecific agent 315B6 inhibits HGF-induced MET activity (Example 3, FIG. 2). Bispecific agent 315B6 inhibits WNT pathway signaling (Example 4, FIG. 3). A bispecific agent comprising an anti-MET antibody and a FZD8-Fc inhibited growth of a lung tumor when combined with taxol (Example 5, FIG. 4).

I. Definitions

To facilitate an understanding of the present invention, a number of terms and phrases are defined below.

The term “antibody” as used herein refers to an immunoglobulin molecule that recognizes and specifically binds a target, such as a protein, polypeptide, peptide, carbohydrate, polynucleotide, lipid, or combinations of the foregoing, through at least one antigen-binding site within the variable region of the immunoglobulin molecule. As used herein, the term encompasses intact polyclonal antibodies, intact monoclonal antibodies, single chain antibodies, antibody fragments (such as Fab, Fab', F(ab')₂, and Fv fragments), single chain Fv (scFv) antibodies, multispecific antibodies such as bispecific antibodies, monospecific antibodies, monovalent antibodies, chimeric antibodies, humanized antibodies, human antibodies, fusion proteins comprising an antigen-binding site of an antibody, and any other modified immunoglobulin molecule comprising an antigen-binding site as long as the antibodies exhibit the desired biological activity. An antibody can be any of the five major classes of immunoglobulins: IgA, IgD, IgE, IgG, and IgM, or subclasses (isotypes) thereof (e.g., IgG1, IgG2, IgG3, IgG4, IgA1, and IgA2), based on the identity of their heavy chain constant domains referred to as alpha, delta, epsilon, gamma, and mu, respectively. The different classes of immunoglobulins have different and well-known subunit structures and three-dimensional configurations. Antibodies can be naked or conjugated to other molecules, including but not limited to, toxins and radioisotopes.

The term “antibody fragment” refers to a portion of an intact antibody and refers to the antigenic determining variable regions of an intact antibody. Examples of antibody fragments include, but are not limited to, Fab, Fab', F(ab')₂, and Fv fragments, linear antibodies, single chain antibodies, and multispecific antibodies formed from antibody fragments. “Antibody fragment” as used herein comprises an antigen-binding site or epitope-binding site.

The term “variable region” of an antibody refers to the variable region of an antibody light chain, or the variable region of an antibody heavy chain, either alone or in combination. The variable region of a heavy or light chain each consist of four framework regions (FR) connected by three complementarity determining regions (CDRs), also known as “hypervariable regions”. The CDRs in each chain are held together in close proximity by the framework regions and, with the CDRs from the other chain, contribute to the formation of the antigen-binding site(s) of the antibody. There are at least two techniques for determining CDRs: (1) an approach based on cross-species sequence variability (i.e., Kabat et al., 1991, *Sequences of Proteins of Immunological Interest*, 5th Edition, National Institutes of Health, Bethesda, Md.), and (2) an approach based on crystallographic studies of antigen-antibody complexes (Al-Lazikani et al., 1997, *J. Mol. Biol.*, 273:927-948). In addition, combinations of these two approaches are sometimes used in the art to determine CDRs.

The term “monoclonal antibody” as used herein refers to a homogeneous antibody population involved in the highly specific recognition and binding of a single antigenic determinant or epitope. This is in contrast to polyclonal antibodies that typically include a mixture of different antibodies directed against a variety of different antigenic determinants. The term “monoclonal antibody” encompasses both intact

and full-length monoclonal antibodies as well as antibody fragments (e.g., Fab, Fab', F(ab')₂, Fv), single chain (scFv) antibodies, fusion proteins comprising an antibody portion, and any other modified immunoglobulin molecule comprising an antigen-binding site. Furthermore, "monoclonal antibody" refers to such antibodies made by any number of techniques, including but not limited to, hybridoma production, phage selection, recombinant expression, and transgenic animals.

The term "humanized antibody" as used herein refers to forms of non-human (e.g., murine) antibodies that are specific immunoglobulin chains, chimeric immunoglobulins, or fragments thereof that contain minimal non-human sequences. Typically, humanized antibodies are human immunoglobulins in which residues of the CDRs are replaced by residues from the CDRs of a non-human species (e.g., mouse, rat, rabbit, or hamster) that have the desired specificity, affinity, and/or binding capability (Jones et al., 1986, *Nature*, 321: 522-525; Riechmann et al., 1988, *Nature*, 332:323-327; Verhoeyen et al., 1988, *Science*, 239:1534-1536). In some instances, the Fv framework region residues of a human immunoglobulin are replaced with the corresponding residues in an antibody from a non-human species that has the desired specificity, affinity, and/or binding capability. The humanized antibody can be further modified by the substitution of additional residues either in the Fv framework region and/or within the replaced non-human residues to refine and optimize antibody specificity, affinity, and/or binding capability. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains containing all or substantially all of the CDRs that correspond to the non-human immunoglobulin whereas all or substantially all of the framework regions are those of a human immunoglobulin consensus sequence. The humanized antibody can also comprise at least a portion of an immunoglobulin constant region or domain (Fc), typically that of a human immunoglobulin. Methods used to generate humanized antibodies are well known in the art.

The term "human antibody" as used herein refers to an antibody produced by a human or an antibody having an amino acid sequence corresponding to an antibody produced by a human. A human antibody may be made using any of the techniques known in the art. This definition of a human antibody specifically excludes a humanized antibody comprising non-human CDRs.

The term "chimeric antibody" as used herein refers to an antibody wherein the amino acid sequence of the immunoglobulin molecule is derived from two or more species. Typically, the variable region of both light and heavy chains corresponds to the variable region of antibodies derived from one species of mammals (e.g., mouse, rat, rabbit, etc.) with the desired specificity, affinity, and/or binding capability, while the constant regions correspond to sequences in antibodies derived from another species (usually human).

The phrase "affinity-matured antibody" as used herein refers to an antibody with one or more alterations in one or more CDRs thereof that result in an improvement in the affinity of the antibody for antigen, compared to a parent antibody that does not possess those alterations(s). The definition also includes alterations in non-CDR residues made in conjunction with alterations to CDR residues. Preferred affinity-matured antibodies will have nanomolar or even picomolar affinities for the target antigen. Affinity-matured antibodies are produced by procedures known in the art. For example, Marks et al., 1992, *Bio/Technology* 10:779-783, describes affinity maturation by VH and VL domain shuffling. Random mutagenesis of CDR and/or framework residues is described

by Barbas et al., 1994, *PNAS*, 91:3809-3813; Schier et al., 1995, *Gene*, 169:147-155; Yelton et al., 1995, *J. Immunol.* 155:1994-2004; Jackson et al., 1995, *J. Immunol.*, 154:3310-9; and Hawkins et al., 1992, *J. Mol. Biol.*, 226:889-896. Site-directed mutagenesis may also be used to obtain affinity-matured antibodies.

The terms "epitope" and "antigenic determinant" are used interchangeably herein and refer to that portion of an antigen capable of being recognized and specifically bound by a particular antibody. When the antigen is a polypeptide, epitopes can be formed both from contiguous amino acids and noncontiguous amino acids juxtaposed by tertiary folding of a protein. Epitopes formed from contiguous amino acids (also referred to as linear epitopes) are typically retained upon protein denaturing, whereas epitopes formed by tertiary folding (also referred to as conformational epitopes) are typically lost upon protein denaturing. An epitope typically includes at least 3, and more usually, at least 5 or 8-10 amino acids in a unique spatial conformation.

The terms "heteromultimeric molecule" or "heteromultimer" or "heteromultimeric complex" or "heteromultimeric polypeptide" are used interchangeably herein to refer to a molecule comprising at least a first polypeptide and a second polypeptide, wherein the second polypeptide differs in amino acid sequence from the first polypeptide by at least one amino acid residue. The heteromultimeric molecule can comprise a "heterodimer" or "heterodimeric agent" formed by the first and second polypeptide or can form higher order tertiary structures where additional polypeptides are present.

The terms "antagonist" and "antagonistic" as used herein refer to any molecule that partially or fully blocks, inhibits, reduces, or neutralizes a biological activity of a target and/or signaling pathway (e.g., the WNT pathway or MET pathway). The term "antagonist" is used herein to include any molecule that partially or fully blocks, inhibits, reduces, or neutralizes the activity of a protein. Suitable antagonist molecules specifically include, but are not limited to, antagonist antibodies, antibody fragments, soluble receptors, or fragments of soluble receptors.

The terms "modulation" and "modulate" as used herein refer to a change or an alteration in a biological activity. Modulation includes, but is not limited to, stimulating or inhibiting an activity. Modulation may be an increase or a decrease in activity (e.g., a decrease in pathway signaling), a change in binding characteristics, or any other change in the biological, functional, or immunological properties associated with the activity of a protein, pathway, or other biological point of interest.

The terms "selectively binds" or "specifically binds" mean that a binding agent or an antibody reacts or associates more frequently, more rapidly, with greater duration, with greater affinity, or with some combination of the above to the epitope, protein, or target molecule than with alternative substances, including unrelated or related proteins. In certain embodiments "specifically binds" means, for instance, that an antibody binds a protein with a K_D of about 0.1 mM or less, but more usually less than about 1 μ M. In certain embodiments, "specifically binds" means that an antibody binds a target at times with a K_D of at least about 0.1 μ M or less, at other times at least about 0.01 μ M or less, and at other times at least about 1 nM or less. Because of the sequence identity between homologous proteins in different species, specific binding can include an antibody that recognizes a protein in more than one species (e.g., human MET and mouse MET). Likewise, because of homology within certain regions of polypeptide sequences of different proteins, specific binding can include an antibody (or other polypeptide or binding agent) that rec-

ognizes more than one protein (e.g., human WNT1 and human WNT7). It is understood that, in certain embodiments, an antibody or binding agent that specifically binds a first target may or may not specifically bind a second target. As such, "specific binding" does not necessarily require (although it can include) exclusive binding, i.e. binding to a single target. Thus, a binding agent may, in certain embodiments, specifically bind more than one target. In certain embodiments, multiple targets may be bound by the same binding site on the agent or antibody. For example, an antibody may, in certain instances, comprise two identical antigen-binding sites, each of which specifically binds the same epitope on two or more proteins. In certain alternative embodiments, an antibody may be bispecific or multispecific and comprise at least two antigen-binding sites with differing specificities. By way of non-limiting example, a bispecific agent may comprise one binding site that recognizes a target on one protein (e.g., human MET) and further comprise a second, different binding site that recognizes a different target on a second protein (e.g., a human WNT protein). Generally, but not necessarily, reference to binding means specific binding.

The terms "polypeptide" and "peptide" and "protein" are used interchangeably herein and refer to polymers of amino acids of any length. The polymer may be linear or branched, it may comprise modified amino acids, and it may be interrupted by non-amino acids. The terms also encompass an amino acid polymer that has been modified naturally or by intervention; for example, disulfide bond formation, glycosylation, lipidation, acetylation, phosphorylation, or any other manipulation or modification, such as conjugation with a labeling component. Also included within the definition are, for example, polypeptides containing one or more analogs of an amino acid (including, for example, unnatural amino acids), as well as other modifications known in the art. It is understood that, because the polypeptides of this invention may be based upon antibodies, in certain embodiments, the polypeptides can occur as single chains or associated chains (e.g., dimers).

The terms "polynucleotide" and "nucleic acid" are used interchangeably herein and refer to polymers of nucleotides of any length, and include DNA and RNA. The nucleotides can be deoxyribonucleotides, ribonucleotides, modified nucleotides or bases, and/or their analogs, or any substrate that can be incorporated into a polymer by DNA or RNA polymerase.

"Conditions of high stringency" may be identified by those that: (1) employ low ionic strength and high temperature for washing, for example 15 mM sodium chloride/1.5 mM sodium citrate/0.1% sodium dodecyl sulfate at 50° C.; (2) employ during hybridization a denaturing agent, such as formamide, for example, 50% (v/v) formamide with 0.1% bovine serum albumin/0.1% Ficoll/0.1% polyvinylpyrrolidone/50 mM sodium phosphate buffer at pH 6.5 in 5×SSC (0.75M NaCl, 75 mM sodium citrate) at 42° C.; or (3) employ during hybridization 50% formamide in 5×SSC, 50 mM sodium phosphate (pH 6.8), 0.1% sodium pyrophosphate, 5×Denhardt's solution, sonicated salmon sperm DNA (50 µl/ml), 0.1% SDS, and 10% dextran sulfate at 42° C., with washes at 42° C. in 0.2×SSC and 50% formamide, followed by a high-stringency wash consisting of 0.1×SSC containing EDTA at 55° C.

The terms "identical" or percent "identity" in the context of two or more nucleic acids or polypeptides, refer to two or more sequences or subsequences that are the same or have a specified percentage of nucleotides or amino acid residues that are the same, when compared and aligned (introducing

gaps, if necessary) for maximum correspondence, not considering any conservative amino acid substitutions as part of the sequence identity. The percent identity may be measured using sequence comparison software or algorithms or by visual inspection. Various algorithms and software that may be used to obtain alignments of amino acid or nucleotide sequences are well-known in the art. These include, but are not limited to, BLAST, ALIGN, Megalign, BestFit, GCG Wisconsin Package, and variations thereof. In some embodiments, two nucleic acids or polypeptides of the invention are substantially identical, meaning they have at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, and in some embodiments at least 95%, 96%, 97%, 98%, 99% nucleotide or amino acid residue identity, when compared and aligned for maximum correspondence, as measured using a sequence comparison algorithm or by visual inspection. In some embodiments, identity exists over a region of the sequences that is at least about 10, at least about 20, at least about 40-60 residues, at least about 60-80 residues in length or any integral value therebetween. In some embodiments, identity exists over a longer region than 60-80 residues, such as at least about 80-100 residues, and in some embodiments the sequences are substantially identical over the full length of the sequences being compared, such as the coding region of a nucleotide sequence.

A "conservative amino acid substitution" is one in which one amino acid residue is replaced with another amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art, including basic side chains (e.g., lysine, arginine, histidine), acidic side chains (e.g., aspartic acid, glutamic acid), uncharged polar side chains (e.g., glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), non-polar side chains (e.g., alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (e.g., threonine, valine, isoleucine) and aromatic side chains (e.g., tyrosine, phenylalanine, tryptophan, histidine). For example, substitution of a phenylalanine for a tyrosine is a conservative substitution. Preferably, conservative substitutions in the sequences of the polypeptides and antibodies of the invention do not abrogate the binding of the polypeptide or antibody containing the amino acid sequence, to the antigen to which the polypeptide or antibody binds. Methods of identifying nucleotide and amino acid conservative substitutions which do not eliminate antigen binding are well-known in the art.

The term "vector" as used herein means a construct, which is capable of delivering, and usually expressing, one or more gene(s) or sequence(s) of interest in a host cell. Examples of vectors include, but are not limited to, viral vectors, naked DNA or RNA expression vectors, plasmid, cosmid, or phage vectors, DNA or RNA expression vectors associated with cationic condensing agents, and DNA or RNA expression vectors encapsulated in liposomes.

As used herein the term "soluble receptor" refers to an N-terminal extracellular domain (or a fragment thereof) of a receptor protein preceding the first transmembrane domain of the receptor that can be secreted from a cell in soluble form.

As used herein the term "FZD soluble receptor" or "soluble FZD receptor" refers to an N-terminal extracellular fragment of a FZD receptor protein preceding the first transmembrane domain of the receptor that can be secreted from a cell in soluble form. FZD soluble receptors comprising the entire N-terminal extracellular domain (ECD) as well as smaller fragments are encompassed by the term. Thus, FZD soluble receptors comprising a FZD Fri domain are also included in this term.

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A polypeptide, antibody, polynucleotide, vector, cell, or composition which is "isolated" is a polypeptide, antibody, polynucleotide, vector, cell, or composition which is in a form not found in nature. Isolated polypeptides, antibodies, polynucleotides, vectors, cells, or compositions include those which have been purified to a degree that they are no longer in a form in which they are found in nature. In some embodiments, a polypeptide, antibody, polynucleotide, vector, cell, or composition which is isolated is substantially pure.

The term "substantially pure" as used herein refers to material which is at least 50% pure (i.e., free from contaminants), at least 90% pure, at least 95% pure, at least 98% pure, or at least 99% pure.

The terms "cancer" and "cancerous" as used herein refer to or describe the physiological condition in mammals in which a population of cells are characterized by unregulated cell growth. Examples of cancer include, but are not limited to, carcinoma, blastoma, sarcoma, and hematologic cancers such as lymphoma and leukemia.

The terms "tumor" and "neoplasm" as used herein refer to any mass of tissue that results from excessive cell growth or proliferation, either benign (non-cancerous) or malignant (cancerous) including pre-cancerous lesions.

The term "metastasis" as used herein refers to the process by which a cancer spreads or transfers from the site of origin to other regions of the body with the development of a similar cancerous lesion at the new location. A "metastatic" or "metastasizing" cell is one that loses adhesive contacts with neighboring cells and migrates (e.g., via the bloodstream or lymph) from the primary site of disease to secondary sites.

The terms "cancer stem cell" and "CSC" and "tumor stem cell" and "tumor initiating cell" are used interchangeably herein and refer to cells from a cancer or tumor that: (1) have extensive proliferative capacity; 2) are capable of asymmetric cell division to generate one or more types of differentiated cell progeny wherein the differentiated cells have reduced and/or limited proliferative or developmental potential; and (3) are capable of symmetric cell divisions for self-renewal or self-maintenance. These properties confer on the cancer stem cells the ability to form or establish a tumor or cancer upon serial transplantation into an immunocompromised host (e.g., a mouse) compared to the majority of tumor cells that fail to form tumors. Cancer stem cells undergo self-renewal versus differentiation in a chaotic manner to form tumors with abnormal cell types that can change over time as mutations occur.

The terms "cancer cell" and "tumor cell" refer to the total population of cells derived from a cancer or tumor or pre-cancerous lesion, including both non-tumorigenic cells, which comprise the bulk of the cancer cell population, and tumorigenic stem cells (cancer stem cells). As used herein, the terms "cancer cell" or "tumor cell" will be modified by the term "non-tumorigenic" when referring solely to those cells lacking the capacity to renew and differentiate to distinguish those tumor cells from cancer stem cells.

The term "tumorigenic" as used herein refers to the functional features of a cancer stem cell including the properties of self-renewal (giving rise to additional tumorigenic cancer stem cells) and proliferation to generate all other tumor cells (giving rise to differentiated and thus non-tumorigenic tumor cells).

The term "tumorigenicity" as used herein refers to the ability of a random sample of cells from the tumor to form palpable tumors upon serial transplantation into immunocompromised hosts (e.g., mice). This definition also includes enriched and/or isolated populations of cancer stem cells that

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form palpable tumors upon serial transplantation into immunocompromised hosts (e.g., mice).

The term "subject" refers to any animal (e.g., a mammal), including, but not limited to, humans, non-human primates, canines, felines, rodents, and the like, which is to be the recipient of a particular treatment. Typically, the terms "subject" and "patient" are used interchangeably herein in reference to a human subject.

The term "pharmaceutically acceptable" refers to a product or compound approved (or approvable) by a regulatory agency of the Federal government or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, including humans.

The terms "pharmaceutically acceptable excipient, carrier or adjuvant" or "acceptable pharmaceutical carrier" refer to an excipient, carrier or adjuvant that can be administered to a subject, together with at least one binding agent of the present disclosure, and which does not destroy the activity of the binding agent. The excipient, carrier or adjuvant should be non-toxic when administered with a binding agent in doses sufficient to deliver a therapeutic effect.

The terms "effective amount" or "therapeutically effective amount" or "therapeutic effect" refer to an amount of a binding agent, an antibody, polypeptide, polynucleotide, small organic molecule, or other drug effective to "treat" a disease or disorder in a subject or mammal. In the case of cancer, the therapeutically effective amount of a drug (e.g., an antibody) has a therapeutic effect and as such can reduce the number of cancer cells; decrease tumorigenicity, tumorigenic frequency or tumorigenic capacity; reduce the number or frequency of cancer stem cells; reduce the tumor size; reduce the cancer cell population; inhibit and/or stop cancer cell infiltration into peripheral organs including, for example, the spread of cancer into soft tissue and bone; inhibit and/or stop tumor or cancer cell metastasis; inhibit and/or stop tumor or cancer cell growth; relieve to some extent one or more of the symptoms associated with the cancer; reduce morbidity and mortality; improve quality of life; or a combination of such effects. To the extent the agent, for example an antibody, prevents growth and/or kills existing cancer cells, it can be referred to as cytostatic and/or cytotoxic.

The terms "treating" or "treatment" or "to treat" or "alleviating" or "to alleviate" refer to both 1) therapeutic measures that cure, slow down, lessen symptoms of, and/or halt progression of a diagnosed pathologic condition or disorder and 2) prophylactic or preventative measures that prevent or slow the development of a targeted pathologic condition or disorder. Thus those in need of treatment include those already with the disorder, those prone to have the disorder; and those in whom the disorder is to be prevented. In some embodiments, a subject is successfully "treated" according to the methods of the present invention if the patient shows one or more of the following: a reduction in the number of or complete absence of cancer cells; a reduction in the tumor size; inhibition of or an absence of cancer cell infiltration into peripheral organs including the spread of cancer cells into soft tissue and bone; inhibition of or an absence of tumor or cancer cell metastasis; inhibition or an absence of cancer growth; relief of one or more symptoms associated with the specific cancer, reduced morbidity and mortality; improvement in quality of life; reduction in tumorigenicity; reduction in the number or frequency of cancer stem cells; or some combination of effects.

As used in the present disclosure and claims, the singular forms "a", "an" and "the" include plural forms unless the context clearly dictates otherwise.

It is understood that wherever embodiments are described herein with the language “comprising” otherwise analogous embodiments described in terms of “consisting of” and/or “consisting essentially of” are also provided. It is also understood that wherever embodiments are described herein with the language “consisting essentially of” otherwise analogous embodiments described in terms of “consisting of” are also provided.

The term “and/or” as used in a phrase such as “A and/or B” herein is intended to include both A and B; A or B; A (alone); and B (alone). Likewise, the term “and/or” as used in a phrase such as “A, B, and/or C” is intended to encompass each of the following embodiments: A, B, and C; A, B, or C; A or C; A or B; B or C; A and C; A and B; B and C; A (alone); B (alone); and C (alone).

II. Met-Binding Agents

The present invention provides agents that specifically bind human MET. The agents are referred to herein as “MET-binding agents”. The phrase “MET-binding agent” encompasses agents that bind only MET and bispecific agents that bind both MET and at least one additional target or antigen. Thus, in some embodiments, the MET-binding agent specifically binds human MET. In some embodiments, the MET-binding agent specifically binds both MET and at least one additional target or antigen. In some embodiments, the MET-binding agent binds both MET and one or more components of the WNT pathway. In some embodiments, the MET-binding agent binds both MET and one or more WNT proteins. In some embodiments, the MET-binding agent binds both MET and one or more FZD proteins. In some embodiments, the MET-binding agent is a polypeptide. In some embodiments, the MET-binding agent is an antibody. In some embodiments, the MET-binding agent is a monovalent antibody. In some embodiments, the MET-binding agent is a heterodimer. In certain embodiments, the MET-binding agent is a bispecific antibody. In certain embodiments, the MET-binding agent is a bispecific agent. In certain embodiments, the MET-binding agent is a bispecific agent comprising a soluble receptor. In certain embodiments, the MET-binding agent is a bispecific agent comprising a monovalent antibody that specifically binds MET. In certain embodiments, the MET-binding agent is a bispecific agent comprising a monovalent antibody that specifically binds MET and a monovalent antibody that specifically binds one or more components of the WNT pathway. In certain embodiments, the MET-binding agent is a bispecific agent (e.g., a heterodimeric agent) comprising a monovalent antibody that specifically binds MET and a soluble receptor that specifically binds one or more WNT proteins.

In certain embodiments, the MET-binding agent specifically binds the extracellular domain of human MET. In some embodiments, the MET-binding agent specifically binds the Sema domain of human MET. In some embodiments, the MET-binding agent specifically binds within the Sema domain of human MET. In some embodiments, the MET-binding agent specifically binds within amino acids 25-932 of human MET (SEQ ID NO:93). In some embodiments, the MET-binding agent specifically binds within amino acids 25-836 of human MET (SEQ ID NO:93). In some embodiments, the MET-binding agent specifically binds within amino acids 25-515 of human MET (SEQ ID NO:93). In some embodiments, the MET-binding agent specifically binds within amino acids 563-836 of human MET (SEQ ID NO:93).

In certain embodiments, the invention provides a MET-binding agent that specifically binds human MET, wherein the MET-binding agent comprises a heavy chain CDR1 com-

prising ASYAWS (SEQ ID NO:1), a heavy chain CDR2 comprising YISYSGGTDYNPSLKS (SEQ ID NO:2), and a heavy chain CDR3 comprising KGAY (SEQ ID NO:3). In some embodiments, the MET-binding agent further comprises a light chain CDR1 comprising SASSSVSSSYLY (SEQ ID NO:4), a light chain CDR2 comprising STSNLAS (SEQ ID NO:5), and a light chain CDR3 comprising HQWSSYPYT (SEQ ID NO:6). In certain embodiments, the MET-binding agent comprises: (a) a heavy chain CDR1 comprising ASYAWS (SEQ ID NO:1), a heavy chain CDR2 comprising YISYSGGTDYNPSLKS (SEQ ID NO:2), and a heavy chain CDR3 comprising KGAY (SEQ ID NO:3), and (b) a light chain CDR1 comprising SASSSVSSSYLY (SEQ ID NO:4), a light chain CDR2 comprising STSNLAS (SEQ ID NO:5), and a light chain CDR3 comprising HQWSSYPYT (SEQ ID NO:6).

In certain embodiments, the invention provides a MET-binding agent that specifically binds human MET, wherein the MET-binding agent comprises: (a) a heavy chain CDR1 comprising ASYAWS (SEQ ID NO: 1), or a variant thereof comprising 1, 2, 3, or 4 amino acid substitutions; (b) a heavy chain CDR2 comprising YISYSGGTDYNPSLKS (SEQ ID NO:2), or a variant thereof comprising 1, 2, 3, or 4 amino acid substitutions; (c) a heavy chain CDR3 comprising KGAY (SEQ ID NO:3), or a variant thereof comprising 1, 2, 3, or 4 amino acid substitutions; (d) a light chain CDR1 comprising SASSSVSSSYLY (SEQ ID NO:4), or a variant thereof comprising 1, 2, 3, or 4 amino acid substitutions; (e) a light chain CDR2 comprising STSNLAS (SEQ ID NO:5), or a variant thereof comprising 1, 2, 3, or 4 amino acid substitutions; and (f) a light chain CDR3 comprising HQWSSYPYT (SEQ ID NO:6), or a variant thereof comprising 1, 2, 3, or 4 amino acid substitutions. In certain embodiments, the amino acid substitutions are conservative substitutions.

In certain embodiments, the invention provides a MET-binding agent that specifically binds MET, wherein the MET-binding agent comprises a heavy chain variable region having at least about 80% sequence identity to SEQ ID NO:7, and a light chain variable region having at least about 80% sequence identity to SEQ ID NO:8. In certain embodiments, the MET-binding agent comprises a heavy chain variable region having at least about 85%, at least about 90%, at least about 95%, at least about 97%, or at least about 99% sequence identity to SEQ ID NO:7. In certain embodiments, the MET-binding agent comprises a light chain variable region having at least about 85%, at least about 90%, at least about 95%, at least about 97%, or at least about 99% sequence identity to SEQ ID NO:8. In certain embodiments, the MET-binding agent comprises a heavy chain variable region having at least about 95% sequence identity to SEQ ID NO:7 and a light chain variable region having at least about 95% sequence identity to SEQ ID NO:8. In certain embodiments, the MET-binding agent comprises a heavy chain variable region comprising SEQ ID NO:7 and a light chain variable region comprising SEQ ID NO:8. In certain embodiments, the MET-binding agent comprises a heavy chain variable region consisting essentially of SEQ ID NO:7 and a light chain variable region consisting essentially of SEQ ID NO:8. In certain embodiments, the MET-binding agent comprises a heavy chain variable region of SEQ ID NO:7 and a light chain variable region of SEQ ID NO:8.

In some embodiments, the invention provides a MET-binding agent that specifically binds MET, wherein the MET-binding agent comprises a heavy chain comprising SEQ ID NO:12 and a light chain comprising SEQ ID NO:14. In some embodiments, the MET-binding agent comprises a heavy chain of SEQ ID NO:12 and a light chain of SEQ ID NO:14.

In some embodiments, the MET-binding agent comprises a heavy chain comprising SEQ ID NO:13 and a light chain comprising SEQ ID NO:14. In some embodiments, the MET-binding agent comprises a heavy chain of SEQ ID NO: 13 and a light chain of SEQ ID NO:14. In some embodiments, the MET-binding agent comprises a heavy chain comprising SEQ ID NO:88 and a light chain comprising SEQ ID NO: 14. In some embodiments, the MET-binding agent comprises a heavy chain of SEQ ID NO:88 and a light chain of SEQ ID NO:14.

In certain embodiments, the invention provides a MET-binding agent that specifically binds human MET, wherein the MET-binding agent comprises one, two, three, four, five, and/or six of the CDRs of antibody 73R009 (see Table 1). In some embodiments, the MET-binding agent comprises one or more of the CDRs of 73R009, two or more of the CDRs of 73R009, three or more of the CDRs of 73R009, four or more of the CDRs of 73R009, five or more of the CDRs of 73R009, or all six of the CDRs of 73R009.

TABLE 1

	73R009
HC CDR1	ASYAWS (SEQ ID NO: 1)
HC CDR2	YISYSGGTDYNPSLKS (SEQ ID NO: 2)
HC CDR3	KGAY (SEQ ID NO: 3)
LC CDR1	SASSSVSSSYLY (SEQ ID NO: 4)
LC CDR2	STSNLAS (SEQ ID NO: 5)
LC CDR3	HQWSSYPYT (SEQ ID NO: 6)

In certain embodiments, a MET-binding agent comprises the heavy chain variable region and the light chain variable region of antibody 73R009. In certain embodiments, a MET-binding agent comprises the heavy chain and the light chain of antibody 73R009 (with or without the leader sequence). In certain embodiments, a MET-binding agent comprises the heavy chain and the light chain of antibody 73R009 (with or without the leader sequence) wherein the heavy chain is modified to promote formation of heterodimers (e.g., bispecific agents) or heteromultimers. In certain embodiments, a MET-binding agent is antibody 73R009. In some embodiments, the MET-binding agent comprises a heavy chain variable region encoded by the plasmid deposited with American Type Culture Collection (ATCC), and designated PTA-13609. In some embodiments, the MET-binding agent comprises a light chain variable region encoded by the plasmid deposited with ATCC and designated PTA-13610.

In certain embodiments, a MET-binding agent comprises, consists essentially of, or consists of, antibody 73R009.

In certain embodiments, a MET-binding agent binds the same epitope or essentially the same epitope on MET as a binding agent of the invention. In another embodiment, a MET-binding agent is an antibody or a bispecific agent that binds an epitope on MET that overlaps with the epitope on MET bound by a binding agent of the invention. In certain embodiments, a MET-binding agent binds the same epitope, or essentially the same epitope, on MET as antibody 73R009. In another embodiment, a MET-binding agent is an antibody

or a bispecific agent that binds an epitope on MET that overlaps with the epitope on MET bound by antibody 73R009.

In certain embodiments, the MET-binding agent is an antibody. In some embodiments, the antibody is a recombinant antibody. In some embodiments, the antibody is a monoclonal antibody. In some embodiments, the antibody is a chimeric antibody. In some embodiments, the antibody is a humanized antibody. In some embodiments, the antibody is a human antibody. In certain embodiments, the antibody is an IgA, IgD, IgE, IgG, or IgM antibody. In certain embodiments, the antibody is an IgG1 antibody. In certain embodiments, the antibody is an IgG2 antibody. In certain embodiments, the antibody is an antibody fragment comprising an antigen-binding site. In some embodiments, the antibody is a bispecific antibody. In some embodiments, the antibody is a monovalent antibody. In some embodiments, the antibody is monospecific. In some embodiment, the antibody is multi-specific.

In some embodiments, the MET-binding agent inhibits binding of MET to hepatocyte growth factor. In some embodiments, the MET-binding agent blocks binding of MET to hepatocyte growth factor. In some embodiments, the MET-binding agent specifically binds MET and facilitates internalization of MET. In some embodiments, the MET-binding agent specifically binds MET and stimulates degradation of MET. In some embodiments, the MET-binding agent specifically binds MET and inhibits dimerization of MET. In some embodiments, the MET-binding agent specifically binds MET and inhibits activation of MET. In some embodiments, the MET-binding agent specifically binds MET and inhibits tumor growth.

In some embodiments, the MET-binding agent binds MET with a K_D of about 100 nM or less. In some embodiments, the MET-binding agent binds MET with a K_D of about 10 nM or less. In some embodiments, the MET-binding agent binds MET with a K_D of about 1 nM or less. In some embodiments, the MET-binding agent binds MET with a K_D of about 0.1 nM or less. In some embodiments, the MET-binding agent binds MET with a K_D of about 0.01 nM or less. In some embodiments, at least one amino acid residue in at least one CDR of the MET-binding agent is substituted with a different amino acid so that the affinity of the MET-binding agent for MET is altered. In some embodiments, the affinity of the MET-binding agent for MET is increased. In some embodiments, the affinity of the MET-binding agent for MET is decreased. In some embodiments, the MET-binding agent binds human MET. In some embodiments, the MET-binding agent binds human MET and mouse MET. In some embodiments, the MET-binding agent binds human MET and does not bind mouse MET.

In certain embodiments, the invention provides a MET-binding agent that is a bispecific agent. In some embodiments, the MET-binding agent is a bispecific agent comprising a first arm and a second arm. In some embodiments, the MET-binding agent is a bispecific agent comprising a first arm and a second arm, wherein the first arm comprises a first binding site that specifically binds MET. In some embodiments, the MET-binding agent is a bispecific agent comprising a first arm and a second arm, wherein the first arm comprises a first binding site that specifically binds MET and the second arm comprises a second binding site that specifically binds a second target or antigen. In some embodiments, the first binding site comprises an antigen-binding site. In some embodiments, the second binding site comprises an antigen-binding site. In some embodiments, the MET-binding agent is a bispecific agent wherein the first arm comprises a first binding site that specifically binds human MET and the sec-

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ond arm comprises a second binding site that binds one or more components of the WNT pathway.

In certain embodiments, the MET-binding agent is a bispecific agent that specifically binds human MET and one or more human FZD proteins. In certain embodiments, the bispecific agent is a bispecific antibody that specifically binds both human MET and one or more human FZD proteins. In some embodiments, the bispecific antibody specifically binds one, two, three, four, five, six, seven, eight, nine, or ten FZD proteins. In some embodiments, the bispecific antibody binds one or more FZD proteins selected from the group consisting of FZD1, FZD2, FZD3, FZD4, FZD5, FZD6, FZD7, FZD8, FZD9, and FZD10. In some embodiments, the bispecific antibody binds one or more FZD proteins comprising FZD1, FZD2, FZD5, FZD7, and/or FZD8. In certain embodiments, the bispecific antibody binds FZD7. In certain embodiments, the bispecific antibody binds FZD5 and/or FZD8. In certain embodiments, the bispecific antibody specifically binds FZD1, FZD2, FZD5, FZD7, and FZD8. Non-limiting examples of FZD-binding agents can be found in U.S. Pat. No. 7,982,013.

In certain embodiments, the bispecific antibody specifically binds MET and the extracellular domain (ECD) of one or more human FZD proteins. In certain embodiments, the bispecific antibody specifically binds MET and a fragment of the extracellular domain (ECD) of one or more human FZD proteins. In certain embodiments, the bispecific antibody specifically binds within the Fri domain (also known as the cysteine-rich domain (CRD)) of one or more human FZD proteins. Sequences of the Fri domain of each of the human FZD proteins are known in the art and are provided as SEQ ID NO:21 (FZD1), SEQ ID NO:22 (FZD2), SEQ ID NO:23 (FZD3), SEQ ID NO:24 (FZD4), SEQ ID NO:25 (FZD5), SEQ ID NO:26 (FZD6), SEQ ID NO:27 (FZD7), SEQ ID NO:28 (FZD8), SEQ ID NO:29 (FZD9), SEQ ID NO:30 (FZD10), SEQ ID NO:31 (FZD10). Sequences of the predicted minimal Fri domains are provided as SEQ ID NO:32 (FZD1), SEQ ID NO:33 (FZD2), SEQ ID NO:34 (FZD3), SEQ ID NO:35 (FZD4), SEQ ID NO:36 (FZD5), SEQ ID NO:37 (FZD6), SEQ ID NO:38 (FZD7), SEQ ID NO:39 (FZD8), SEQ ID NO:40 (FZD9) and SEQ ID NO:41 (FZD10).

In certain embodiments, the bispecific antibody binds human MET and binds one, two, three, four, five, or more FZD proteins. In some embodiments, the bispecific antibody specifically binds human MET and binds one, two, three, four, or five FZD proteins selected from the group consisting of FZD1, FZD2, FZD5, FZD7, and FZD8. In some embodiments, the bispecific antibody specifically binds MET and binds at least FZD5 and FZD8.

In certain embodiments, the bispecific antibody that binds human MET and one or more human FZD proteins is a FZD antagonist. In certain embodiments, the bispecific antibody is a Wnt pathway antagonist. In certain embodiments, the bispecific antibody inhibits Wnt signaling. In some embodiments, the bispecific antibody inhibits canonical Wnt signaling.

In certain embodiments, the MET-binding agent is a bispecific agent that specifically binds human MET and one or more human WNT proteins. In certain embodiments, the bispecific agent is a bispecific antibody that specifically binds human MET and one or more human WNT proteins. In certain embodiments, the bispecific antibody specifically binds human MET and binds one, two, three, four, five, six, seven, eight, nine, ten, or more WNT proteins. In some embodiments, the bispecific antibody binds human MET and binds one or more human WNT proteins selected from the group consisting of WNT1, WNT2, WNT2b, WNT3, WNT3a,

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WNT4, WNT5a, WNT5b, WNT6, WNT7a, WNT7b, WNT8a, WNT8b, WNT9a, WNT9b, WNT10a, WNT10b, WNT11, and WNT16. In certain embodiments, the bispecific antibody binds human MET and binds one or more (or two or more, three or more, four or more, five or more, etc.) WNT proteins selected from the group consisting of WNT1, WNT2, WNT2b, WNT3, WNT3a, WNT7a, WNT7b, WNT8a, WNT8b, WNT10a, and WNT10b. In certain embodiments, the one or more (or two or more, three or more, four or more, five or more, etc.) WNT proteins are selected from the group consisting of WNT1, WNT2, WNT2b, WNT3, WNT3a, WNT8a, WNT8b, WNT10a, and WNT10b. Non-limiting examples of WNT-binding agents can be found in International Publication WO 2011/088127.

In certain embodiments, the bispecific antibody specifically binds MET and the C-terminal cysteine rich domain (CRD) of one or more human WNT proteins. In certain embodiments, the bispecific antibody binds a domain within one or more WNT proteins selected from the group consisting of: SEQ ID NO:57 (WNT1), SEQ ID NO:58 (WNT2), SEQ ID NO:59 (WNT2b), SEQ ID NO:60 (WNT3), SEQ ID NO:61 (WNT3a), SEQ ID NO:62 (WNT7a), SEQ ID NO:63 (WNT7b), SEQ ID NO:64 (WNT8a), SEQ ID NO:65 (WNT8b), SEQ ID NO:66 (WNT10a), and SEQ ID NO:67 (WNT10b).

In certain embodiments, the bispecific antibody that binds human MET and one or more WNT proteins is a WNT antagonist. In certain embodiments, the bispecific antibody is a WNT pathway antagonist. In certain embodiments, the bispecific antibody inhibits WNT signaling. In some embodiments, the bispecific antibody inhibits canonical WNT signaling.

In certain embodiments, the MET-binding agent is a bispecific agent that specifically binds human MET and one or more human WNT proteins. In certain embodiments, the bispecific agent that specifically binds human MET and one or more human WNT proteins is a heterodimeric agent. In certain embodiments, the bispecific agent that specifically binds human MET and one or more human WNT proteins is a heterodimeric agent comprising a soluble receptor. In certain embodiments, the bispecific agent that specifically binds human MET and one or more human WNT proteins is a heterodimeric agent comprising a fusion protein. In certain embodiments, the bispecific agent that specifically binds human MET and one or more human WNT proteins is a heterodimeric agent comprising a first arm comprising a monovalent antibody and a second arm comprising a soluble receptor. In certain embodiments, the bispecific agent that specifically binds human MET and one or more human WNT proteins is a heterodimeric agent comprising a first arm comprising a monovalent antibody and a second arm comprising a fusion protein.

In certain embodiments, the MET-binding agent is a bispecific agent that specifically binds human MET and one or more human WNT proteins, wherein the bispecific agent comprises the extracellular domain (ECD) of a FZD receptor protein (e.g., a soluble receptor). In certain embodiments, the FZD protein is a human FZD protein. In certain embodiments, the human FZD protein is FZD1, FZD2, FZD3, FZD4, FZD5, FZD6, FZD7, FZD8, FZD9, or FZD10. In certain embodiments, the human FZD protein is FZD8. Non-limiting examples of soluble FZD receptors can be found in U.S. Pat. Nos. 7,723,477 and 7,947,277; and U.S. Patent Publication No. 2011/0305695.

In some embodiments, the bispecific agent comprises a Fri domain of an ECD of a FZD protein. The Fri domains for each of the human FZD1-10 proteins are provided as SEQ ID

NOs:21-31. The minimal (or core) Fri domains for each of the human FZD1-10 proteins are provided as SEQ ID NOs:32-41. Those of skill in the art may differ in their understanding of the exact amino acids corresponding to the various Fri domains. Thus, the N-terminus and/or C-terminus of the domains outlined above and herein may extend or be shortened by 1, 2, 3, 4, 5, 6, 7, 8, 9, or even 10 amino acids.

In some embodiments, a soluble receptor comprising a FZD Fri domain can demonstrate altered biological activity (e.g., increased protein half-life) compared to a soluble receptor comprising the entire FZD ECD. In some embodiments, protein half-life can be further increased by covalent modification with polyethylene glycol (PEG) or polyethylene oxide (PEO).

In certain embodiments, the bispecific agent comprises a Fri domain of a human FZD protein, or a fragment or variant of the Fri domain that binds one or more human WNT proteins. In certain embodiments, the human FZD protein is FZD1, FZD2, FZD3, FZD4, FZD5, FZD6, FZD7, FZD8, FZD9, or FZD10. In certain embodiments, the human FZD protein is FZD8. In certain embodiments, the human FZD protein is FZD4. In certain embodiments, the human FZD protein is FZD5. In certain embodiments, the human FZD protein is FZD10. In certain embodiments, the FZD protein is FZD4 and the bispecific agent comprises SEQ ID NO:24. In certain embodiments, the FZD protein is FZD5 and the bispecific agent comprises SEQ ID NO:25. In certain embodiments, the FZD protein is FZD7 and the bispecific agent comprises SEQ ID NO:27. In certain embodiments, the FZD protein is FZD8 and the bispecific agent comprises SEQ ID NO:28 or SEQ ID NO:29. In certain embodiments, the FZD protein is FZD10 and the bispecific agent comprises SEQ ID NO:31.

In some embodiments, the bispecific agent comprises a Fri domain comprising the minimal Fri domain of FZD1 (SEQ ID NO:32), the minimal Fri domain of FZD2 (SEQ ID NO:33), the minimal Fri domain of FZD3 (SEQ ID NO:34), the minimal Fri domain of FZD4 (SEQ ID NO:35), the minimal Fri domain of FZD5 (SEQ ID NO:36), the minimal Fri domain of FZD6 (SEQ ID NO:37), the minimal Fri domain of FZD7 (SEQ ID NO:38), the minimal Fri domain of FZD8 (SEQ ID NO:39), the minimal Fri domain of FZD9 (SEQ ID NO:40), or the minimal Fri domain of FZD10 (SEQ ID NO:41). In some embodiments, the bispecific agent comprises a Fri domain comprising the minimal Fri domain of FZD8 (SEQ ID NO:39).

In some embodiments, the bispecific agent comprises a Fri domain consisting essentially of the Fri domain of FZD1, the Fri domain of FZD2, the Fri domain of FZD3, the Fri domain of FZD4, the Fri domain of FZD5, the Fri domain of FZD6, the Fri domain of FZD7, the Fri domain of FZD8, the Fri domain of FZD9, or the Fri domain of FZD10. In some embodiments, the bispecific agent comprises a Fri domain consisting essentially of the Fri domain of FZD8.

In some embodiments, the bispecific agent comprises a sequence selected from the group consisting of: SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, and SEQ ID NO:41. In some embodiments, the bispecific agent comprises a Fri domain comprising SEQ ID NO:39. In some embodiments, the bispecific agent comprises a Fri domain comprising SEQ ID NO:28. In some embodiments, the bispecific agent comprises a Fri domain of SEQ ID NO:28. In some embodiments, the

bispecific agent comprises a Fri domain comprising SEQ ID NO:29. In some embodiments, the bispecific agent comprises a Fri domain of SEQ ID NO:29.

In certain embodiments, the bispecific agent comprises a variant of any one of the aforementioned FZD Fri domain sequences that comprises one or more (e.g., one, two, three, four, five, six, seven, eight, nine, ten, etc.) conservative substitutions and is capable of binding WNT protein(s).

In certain embodiments, a bispecific agent, such as an agent comprising a soluble FZD receptor, further comprises a heterologous polypeptide. In some embodiments, a soluble FZD receptor may include FZD ECD or Fri domains linked to other heterologous functional and structural polypeptides including, but not limited to, a human Fc region, protein tags (e.g., myc, FLAG, GST), other endogenous proteins or protein fragments, or any other useful protein sequence including any linker region between a FZD ECD or Fri domain and a second polypeptide. In certain embodiments, the heterologous polypeptide comprises a human Fc region. The Fc region can be obtained from any of the classes of immunoglobulin, IgG, IgA, IgM, IgL) and IgE. In some embodiments, the Fc region is a human IgG1 Fc region. In some embodiments, the Fc region is a human IgG2 Fc region. In some embodiments, the Fc region is a wild-type Fc region (including Fc region variants found in nature). In some embodiments, the Fc region is a mutated Fc region. In some embodiments, the Fc region is truncated at the N-terminal end by 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more amino acids, (e.g., in the hinge domain). In some embodiments, an amino acid in the hinge domain is changed to hinder undesirable disulfide bond formation. In some embodiments, a cysteine is replaced with a serine to hinder or block undesirable disulfide bond formation. In some embodiments, the Fc region is truncated at the C-terminal end by 1, 2, 3, or more amino acids. In some embodiments, the Fc region is truncated at the C-terminal end by 1 amino acid. In certain embodiments, the heterologous polypeptide comprises SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:91, or SEQ ID NO:92. In certain embodiments, the heterologous polypeptide is SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:91, or SEQ ID NO:92. In certain embodiments, the heterologous polypeptide comprises SEQ ID NO:48, SEQ ID NO:51, or SEQ ID NO:52. In certain embodiments, the heterologous polypeptide is SEQ ID NO:48, SEQ ID NO:51, or SEQ ID NO:52.

In certain embodiments, a bispecific agent comprises a fusion protein comprising at least a minimal Fri domain of a FZD receptor and a Fc region. As used herein, a "fusion protein" is a hybrid protein expressed by a nucleic acid molecule comprising nucleotide sequences of at least two genes. In some embodiments, the C-terminus of the first polypeptide is linked to the N-terminus of the immunoglobulin Fc region. In some embodiments, the first polypeptide (e.g., a FZD Fri domain) is directly linked to the Fc region (i.e. without an intervening linker). In some embodiments, the first polypeptide is linked to the Fc region via a linker.

As used herein, the term "linker" refers to a linker inserted between a first polypeptide (e.g., a FZD component) and a second polypeptide (e.g., a Fc region). In some embodiments, the linker is a peptide linker. Linkers should not adversely affect the expression, secretion, or bioactivity of the polypeptide. Linkers should not be antigenic and should not elicit an immune response. Suitable linkers are known to those of skill

in the art and often include mixtures of glycine and serine residues and often include amino acids that are sterically unhindered. Other amino acids that can be incorporated into useful linkers include threonine and alanine residues. Linkers can range in length, for example from 1-50 amino acids in length, 1-22 amino acids in length, 1-10 amino acids in length, 1-5 amino acids in length, or 1-3 amino acids in length. Linkers may include, but are not limited to, SerGly, GGSG, GSGS, GGGS, S(GGS)_n where n is 1-7, GRA, poly (Gly), poly(Ala), ESGGGGV (SEQ ID NO:68), LESGGGGVT (SEQ ID NO:69), GRAQVT (SEQ ID NO:70), WRAQVT (SEQ ID NO:71), and ARGRAQVT (SEQ ID NO:72). As used herein, a linker is an intervening peptide sequence that does not include amino acid residues from either the C-terminus of the first polypeptide (e.g., a FZD Fri domain) or the N-terminus of the second polypeptide (e.g., the Fc region).

In some embodiments, the bispecific agent comprises a FZD Fri domain, a Fc region and a linker connecting the FZD Fri domain to the Fc region. In some embodiments, the FZD Fri domain comprises SEQ ID NO:28, SEQ ID NO:29, or SEQ ID NO:39. In some embodiments, the linker comprises ESGGGGV (SEQ ID NO:68) or LESGGGGVT (SEQ ID NO:69).

FZD receptors and immunoglobulin proteins contain signal sequences that direct the transport of the proteins. Signal sequences (also referred to as signal peptides or leader sequences) are located at the N-terminus of nascent polypeptides. They target the polypeptide to the endoplasmic reticulum and the proteins are sorted to their destinations, for example, to the inner space of an organelle, to an interior membrane, to the cell's outer membrane, or to the cell exterior via secretion. Most signal sequences are cleaved from the protein by a signal peptidase after the proteins are transported to the endoplasmic reticulum. The cleavage of the signal sequence from the polypeptide usually occurs at a specific site in the amino acid sequence and is dependent upon amino acid residues within the signal sequence. Although there is usually one specific cleavage site, more than one cleavage site may be recognized and/or used by a signal peptidase resulting in a non-homogenous N-terminus of the polypeptide. For example, the use of different cleavage sites within a signal sequence can result in a polypeptide expressed with different N-terminal amino acids. Accordingly, in some embodiments, the polypeptides as described herein may comprise a mixture of polypeptides with different N-termini. In some embodiments, the N-termini differ in length by 1, 2, 3, 4, or 5 amino acids. In some embodiments, the polypeptide is substantially homogeneous, i.e., the polypeptides have the same N-terminus. In some embodiments, the signal sequence of the polypeptide comprises one or more (e.g., one, two, three, four, five, six, seven, eight, nine, ten, etc.) amino acid substitutions and/or deletions. In some embodiments, the signal sequence of the polypeptide comprises amino acid substitutions and/or deletions that allow one cleavage site to be dominant, thereby resulting in a substantially homogeneous polypeptide with one N-terminus.

In some embodiments, the bispecific agent that specifically binds MET and one or more WNT proteins comprises: a first polypeptide comprising SEQ ID NO:28 and a second polypeptide comprising SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, or SEQ ID NO:52. In some embodiments, the bispecific agent comprises: a first polypeptide comprising SEQ ID NO:28 and a second polypeptide comprising SEQ ID NO:47 or SEQ ID NO:48. In some embodiments, the bispecific agent comprises: a first polypeptide comprising SEQ ID NO:28 and a

second polypeptide comprising SEQ ID NO:49 or SEQ ID NO:51. In some embodiments, the bispecific agent comprises: a first polypeptide comprising SEQ ID NO:28 and a second polypeptide comprising SEQ ID NO:50 or SEQ ID NO:52. In some embodiments, the bispecific agent comprises: a first polypeptide comprising SEQ ID NO:28 and a second polypeptide comprising SEQ ID NO:52. In some embodiments, the bispecific agent that specifically binds MET and one or more WNT proteins comprises: a first polypeptide comprising SEQ ID NO:29 and a second polypeptide comprising SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, or SEQ ID NO:52. In some embodiments, the bispecific agent comprises: a first polypeptide comprising SEQ ID NO:29 and a second polypeptide comprising SEQ ID NO:47 or SEQ ID NO:48. In some embodiments, the bispecific agent comprises: a first polypeptide comprising SEQ ID NO:29 and a second polypeptide comprising SEQ ID NO:49 or SEQ ID NO:51. In some embodiments, the bispecific agent comprises: a first polypeptide comprising SEQ ID NO:29 and a second polypeptide comprising SEQ ID NO:50 or SEQ ID NO:52. In some embodiments, the bispecific agent comprises: a first polypeptide comprising SEQ ID NO:29 and a second polypeptide comprising SEQ ID NO:52. In some embodiments, the bispecific agent that specifically binds MET and one or more WNT proteins comprises: a first polypeptide comprising SEQ ID NO:39 and a second polypeptide comprising SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, or SEQ ID NO:52. In some embodiments, the bispecific agent comprises: a first polypeptide comprising SEQ ID NO:39 and a second polypeptide comprising SEQ ID NO:47 or SEQ ID NO:48. In some embodiments, the bispecific agent comprises: a first polypeptide comprising SEQ ID NO:39 and a second polypeptide comprising SEQ ID NO:49 or SEQ ID NO:51. In some embodiments, the bispecific agent comprises: a first polypeptide comprising SEQ ID NO:39 and a second polypeptide comprising SEQ ID NO:50 or SEQ ID NO:52. In some embodiments, the bispecific agent comprises: a first polypeptide comprising SEQ ID NO:39 and a second polypeptide comprising SEQ ID NO:52.

In some embodiments, the bispecific agent comprises SEQ ID NO:55 or SEQ ID NO:56. In some embodiments, the bispecific agent comprises SEQ ID NO:56. In some embodiments, the bispecific agent comprises SEQ ID NO:87.

In some embodiments, the MET-binding agent is a bispecific agent comprising: (a) a first binding site that specifically binds human MET, and (b) a second binding site that binds one or more components of the WNT pathway, wherein the first binding site comprises (a) a heavy chain CDR1 comprising ASYAWS (SEQ ID NO: 1), a heavy chain CDR2 comprising YISYSGGTDYNPSLKS (SEQ ID NO:2), and a heavy chain CDR3 comprising KGAY (SEQ ID NO:3), and (b) a light chain CDR1 comprising SASSSVSSSYLY (SEQ ID NO:4), a light chain CDR2 comprising STSNLAS (SEQ ID NO:5), and a light chain CDR3 comprising HQWSSYPYT (SEQ ID NO:6). In some embodiments, the MET-binding agent is a bispecific agent comprising: (a) a first binding site that specifically binds human MET, and (b) a second binding site that binds one or more WNT proteins, wherein the first binding site comprises (a) a heavy chain CDR1 comprising ASYAWS (SEQ ID NO:1), a heavy chain CDR2 comprising YISYSGGTDYNPSLKS (SEQ ID NO:2), and a heavy chain CDR3 comprising KGAY (SEQ ID NO:3), and (b) a light chain CDR1 comprising SASSSVSSSYLY (SEQ

ID NO:4), a light chain CDR2 comprising STSNLAS (SEQ ID NO:5), and a light chain CDR3 comprising HQWSSYPYT (SEQ ID NO:6).

In some embodiments, the MET-binding agent is a bispecific agent comprising (a) a first binding site that specifically binds human MET and (b) a second binding site that binds one or more components of the WNT pathway, wherein the first binding site comprises a heavy chain CDR1 comprising GYTFTSYWLH (SEQ ID NO:78), a heavy chain CDR2 comprising GMIDPSNSDTRFNPFKD (SEQ ID NO:79), and a heavy chain CDR3 comprising TYGSYVSPLDY (SEQ ID NO:81), SYGSYVSPLDY (SEQ ID NO:82), ATYG-SYVSPLDY (SEQ ID NO:83), or XYGSYVSPLDY (SEQ ID NO:80), wherein X is not R; and a light chain CDR1 comprising KSSQSLLYTSSQKNYLA (SEQ ID NO:84), a light chain CDR2 comprising WASTRES (SEQ ID NO:85), and a light chain CDR3 comprising QQYYAYPWT (SEQ ID NO:86).

In some embodiments, the MET-binding agent is a bispecific agent comprising: (a) a first binding site that specifically binds human MET, and (b) a second binding site that binds one or more components of the WNT pathway, wherein the first binding site comprises a heavy chain variable region having at least about 80% sequence identity to SEQ ID NO:7. In some embodiments, the first binding site further comprises a light chain variable region having at least about 80% sequence identity to SEQ ID NO:8. In certain embodiments, the first binding site comprises a heavy chain variable region having at least about 85%, at least about 90%, at least about 95%, at least about 97%, or at least about 99% sequence identity to SEQ ID NO:7, and a light chain variable region having at least about 85%, at least about 90%, at least about 95%, at least about 97%, or at least about 99% sequence identity to SEQ ID NO:8.

In some embodiments, the MET-binding agent is a bispecific agent that comprises (a) a first arm comprising a first binding site that specifically binds human MET, and (b) a second arm comprising a second binding site that binds one or more WNT proteins, wherein the first arm comprises a heavy chain CDR1 comprising ASYAWS (SEQ ID NO:1), a heavy chain CDR2 comprising YISYSGGTDYNPSLKS (SEQ ID NO:2), and a heavy chain CDR3 comprising KGAY (SEQ ID NO:3), and a light chain CDR1 comprising SASSSVSS-SYLY (SEQ ID NO:4), a light chain CDR2 comprising STSNLAS (SEQ ID NO:5), and a light chain CDR3 comprising HQWSSYPYT (SEQ ID NO:6); and the second arm comprises a FZD8 Fri domain. In some embodiments, the second arm comprises SEQ ID NO:28, SEQ ID NO:29, or SEQ ID NO:39.

In some embodiments, the MET-binding agent is a bispecific agent that specifically binds human MET and binds one or more components of the WNT pathway, wherein the first arm of the bispecific agent comprises a heavy chain of SEQ ID NO:12, SEQ ID NO:13, or SEQ ID NO:88, and/or a light chain of SEQ ID NO: 14. In some embodiments, the first arm of the bispecific agent comprises a heavy chain of SEQ ID NO: 13 and a light chain of SEQ ID NO:14.

In some embodiments, the MET-binding agent is a bispecific agent that specifically binds human MET and binds one or more WNT proteins, wherein the first arm of the bispecific agent comprises a heavy chain of SEQ ID NO:12, SEQ ID NO:13, or SEQ ID NO:88, and a light chain of SEQ ID NO:14, and wherein the second arm of the bispecific agent comprises a first polypeptide comprising a FZD8 Fri domain. In some embodiments, the second arm of the bispecific agent comprises a first polypeptide comprising a FZD8 Fri domain and a second polypeptide comprising a human Fc region. In

some embodiments, the second arm of the bispecific agent comprises a first polypeptide comprising a FZD8 Fri domain and a second polypeptide comprising a human IgG1 Fc region. In some embodiments, the second arm of the bispecific agent comprises a first polypeptide comprising a FZD8 Fri domain and a second polypeptide comprising a human IgG2 Fc region. In some embodiments, the second arm of the bispecific agent comprises SEQ ID NO:28, SEQ ID NO:29, or SEQ ID NO:39. In some embodiments, the second arm of the bispecific agent comprises a first polypeptide comprising SEQ ID NO:28, SEQ ID NO:29, or SEQ ID NO:39 and a second polypeptide comprising SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, or SEQ ID NO:52.

In some embodiments, the MET-binding agent is a bispecific agent that specifically binds human MET and binds one or more WNT proteins, wherein the first arm of the bispecific agent comprises a heavy chain of SEQ ID NO: 13 and a light chain of SEQ ID NO: 14, and the second arm of the bispecific agent comprises a first polypeptide of SEQ ID NO:28 and a second polypeptide of SEQ ID NO:52. In some embodiments, the MET-binding agent is a bispecific agent that specifically binds human MET and binds one or more WNT proteins, wherein the first arm of the bispecific agent comprises a heavy chain of SEQ ID NO:13 and a light chain of SEQ ID NO:14, and the second arm of the bispecific agent comprises SEQ ID NO:56. In some embodiments, the bispecific agent is referred to as bispecific agent 315B6. Bispecific agent 315B6 comprises (a) a heavy chain encoded by the plasmid comprising SEQ ID NO:16 deposited with ATCC, 10801 University Boulevard, Manassas, Va., USA, under the conditions of the Budapest Treaty on Mar. 12, 2013 and assigned designation number PTA-13609, (b) a light chain encoded by the plasmid comprising SEQ ID NO:19 deposited with ATCC under the conditions of the Budapest Treaty on Mar. 12, 2013 and assigned designation number PTA-13610; and (c) a polypeptide encoded by the plasmid comprising SEQ ID NO:89 deposited with ATCC under the conditions of the Budapest Treaty on Mar. 12, 2013 and assigned designation number PTA-13611. Bispecific agent 315B6 comprises (a) a heavy chain comprising SEQ ID NO:13 encoded by the plasmid deposited with ATCC and assigned designation number PTA-13609, (b) a light chain comprising SEQ ID NO:14 encoded by the plasmid deposited with ATCC and assigned designation number PTA-13610; and (c) a polypeptide comprising SEQ ID NO:56 encoded by the plasmid deposited with ATCC and assigned designation number PTA-13611.

In some embodiments, the bispecific agent comprises a heavy chain comprising the heavy chain variable region encoded by the plasmid deposited with ATCC designated PTA-13609 and a light chain comprising the light chain variable region encoded by the plasmid deposited with ATCC designated PTA-13610. In some embodiments, the bispecific agent comprises a polypeptide encoded by the plasmid deposited with ATCC designated PTA-13611.

In some embodiments, the MET-binding agent is a bispecific agent that specifically binds human MET and binds one or more WNT proteins, wherein the first arm of the bispecific agent comprises a heavy chain of SEQ ID NO:88 and a light chain of SEQ ID NO: 14, and wherein the second arm of the bispecific agent comprises a first polypeptide of SEQ ID NO:28 and a second polypeptide of SEQ ID NO:50. In some embodiments, the MET-binding agent is a bispecific agent that specifically binds human MET and binds one or more WNT proteins, wherein the first arm of the bispecific agent comprises a heavy chain of SEQ ID NO:88 and a light chain of SEQ ID NO: 14, and wherein the second arm of the bispecific agent comprises SEQ ID NO:87.

In some embodiments, the MET-binding agent is a bispecific agent that specifically binds human MET and binds one or more WNT proteins, wherein the first arm of the bispecific agent comprises a heavy chain variable region having at least about 80% sequence identity to SEQ ID NO:7 and a light chain variable region having at least about 80% sequence identity to SEQ ID NO:8, and the second arm of the bispecific agent comprises a FZD8 Fri domain. In certain embodiments, the first arm of the bispecific agent comprises a heavy chain variable region having at least about 85%, at least about 90%, at least about 95%, at least about 97%, or at least about 99% sequence identity to SEQ ID NO:7 and a light chain variable region having at least about 85%, at least about 90%, at least about 95%, at least about 97%, or at least about 99% sequence identity to SEQ ID NO:8, and the second arm of the bispecific agent comprises a FZD8 Fri domain. In certain embodiments, the first arm of the bispecific agent comprises a heavy chain variable region having at least about 95% sequence identity to SEQ ID NO:7 and a light chain variable region having at least about 95% sequence identity to SEQ ID NO:8, and the second arm of the bispecific agent comprises a FZD8 Fri domain. In certain embodiments, the first arm of the bispecific agent comprises a heavy chain variable region comprising SEQ ID NO:7 and a light chain variable region comprising SEQ ID NO:8, and the second arm of the bispecific agent comprises a FZD8 Fri domain. In certain embodiments, the first arm of the bispecific agent comprises a heavy chain variable region of SEQ ID NO:7 and a light chain variable region of SEQ ID NO:8, and the second arm of the bispecific agent comprises a FZD8 Fri domain.

In some embodiments, the MET-binding agent is a bispecific agent, wherein the first arm of the bispecific agent comprises a first CH3 domain and the second arm of the bispecific agent comprises a second CH3 domain, and each of the CH3 domains is modified to promote formation of heterodimers or heteromultimers. In some embodiments, the first and second CH3 domains are modified using a knobs-into-holes technique. In some embodiments, the first and second CH3 domains comprise changes or substitutions in amino acids that result in altered electrostatic interactions. In some embodiments, the first and second CH3 domains comprise changes in amino acids that result in altered hydrophobic/hydrophilic interactions.

In some embodiments, the MET-binding agent is a bispecific agent that comprises two heavy chain constant regions selected from the group consisting of: (a) a first human IgG1 constant region, wherein the amino acids at positions corresponding to positions 253 and 292 of SEQ ID NO:74 are substituted with glutamate or aspartate, and a second human IgG1 constant region, wherein the amino acids at positions corresponding to positions 240 and 282 of SEQ ID NO:74 are substituted with lysine; (b) a first human IgG2 constant region, wherein the amino acids at positions corresponding to positions 249 and 288 of SEQ ID NO:75 are substituted with glutamate or aspartate, and a second human IgG2 constant region wherein the amino acids at positions corresponding to positions 236 and 278 of SEQ ID NO:75 are substituted with lysine; (c) a first human IgG3 constant region, wherein the amino acids at positions corresponding to positions 300 and 339 of SEQ ID NO:76 are substituted with glutamate or aspartate, and a second human IgG3 constant region wherein the amino acids at positions corresponding to positions 287 and 329 of SEQ ID NO:76 are substituted with lysine; and (d) a first human IgG4 constant region, wherein the amino acids at positions corresponding to positions 250 and 289 of SEQ ID NO:77 are substituted with glutamate or aspartate, and a second IgG4 constant region wherein the amino acids at

positions corresponding to positions 237 and 279 of SEQ ID NO:78 are substituted with lysine.

In some embodiments, the bispecific agent comprises a first human IgG1 constant region with amino acid substitutions at positions corresponding to positions 253 and 292 of SEQ ID NO:74, wherein the amino acids are replaced with glutamate or aspartate, and a second human IgG1 constant region with amino acid substitutions at positions corresponding to positions 240 and 282 of SEQ ID NO:74, wherein the amino acids are replaced with lysine. In some embodiments, the bispecific agent comprises a first human IgG2 constant region with amino acid substitutions at positions corresponding to positions 249 and 288 of SEQ ID NO:75, wherein the amino acids are replaced with glutamate or aspartate, and a second human IgG2 constant region with amino acid substitutions at positions corresponding to positions 236 and 278 of SEQ ID NO:75, wherein the amino acids are replaced with lysine. In some embodiments, the bispecific agent comprises a first human IgG3 constant region with amino acid substitutions at positions corresponding to positions 300 and 339 of SEQ ID NO:76, wherein the amino acids are replaced with glutamate or aspartate, and a second human IgG3 constant region with amino acid substitutions at positions corresponding to positions 287 and 329 of SEQ ID NO:76, wherein the amino acids are replaced with lysine. In some embodiments, the bispecific agent comprises a first human IgG4 constant region with amino acid substitutions at positions corresponding to positions 250 and 289 of SEQ ID NO:77, wherein the amino acids are replaced with glutamate or aspartate, and a second human IgG4 constant region with amino acid substitutions at positions corresponding to positions 237 and 279 of SEQ ID NO:77, wherein the amino acids are replaced with lysine.

In some embodiments, the bispecific agent comprises a first human IgG2 constant region with amino acid substitutions at positions corresponding to positions 249 and 288 of SEQ ID NO:75, wherein the amino acids are replaced with glutamate, and a second human IgG2 constant region with amino acid substitutions at positions corresponding to positions 236 and 278 of SEQ ID NO:75, wherein the amino acids are replaced with lysine. In some embodiments, the bispecific agent comprises a first human IgG2 constant region with amino acid substitutions at positions corresponding to positions 249 and 288 of SEQ ID NO:75, wherein the amino acids are replaced with aspartate, and a second human IgG2 constant region with amino acid substitutions at positions corresponding to positions 236 and 278 of SEQ ID NO:75, wherein the amino acids are replaced with lysine.

In certain embodiments, a MET-binding agent binds MET and/or one or more components of the WNT pathway with a dissociation constant (K_D) of about 1 μ M or less, about 100 nM or less, about 40 nM or less, about 20 nM or less, about 10 nM or less, about 1 nM or less, or about 0.1 nM or less. In some embodiments, a MET-binding agent binds MET and/or one or more components of the WNT pathway with a K_D of about 20 nM or less. In some embodiments, a MET-binding agent binds MET and/or one or more components of the WNT pathway with a K_D of about 10 nM or less. In some embodiments, a MET-binding agent binds MET and/or one or more components of the WNT pathway with a K_D of about 1 nM or less. In some embodiments, a MET-binding agent binds both human MET and mouse MET with a K_D of about 100 nM or less. In some embodiments, a MET-binding agent binds both human MET and mouse MET with a K_D of about 50 nM or less. In some embodiments, a

MET-binding agent binds human MET and does not bind mouse MET. In some embodiments, a MET-binding agent binds one or more human WNT proteins with a K_D of about 100 nM or less. In some embodiments, a MET-binding agent binds one or more human WNT proteins with a K_D of about 50 nM or less. In some embodiments, a MET-binding agent binds one or more human WNT proteins with a K_D of about 20 nM or less. In some embodiments, the dissociation constant of the binding agent (e.g., an antibody or bispecific agent) to MET is the dissociation constant determined using a MET fusion protein comprising at least a portion of MET immobilized on a Biacore chip. In some embodiments, the dissociation constant of the binding agent (e.g., an antibody or bispecific agent) to a WNT protein is the dissociation constant determined using a WNT-fusion protein comprising at least a portion of a WNT protein immobilized on a Biacore chip.

In some embodiments, the MET-binding agent is a bispecific agent that comprises a first binding site that specifically binds MET and a second binding site that specifically binds one or more components of the WNT pathway. In some embodiments, a MET-binding agent binds both MET and one or more components of the WNT pathway (e.g., WNT proteins or FZD proteins) with a K_D of about 100 nM or less. In some embodiments, a MET-binding agent binds both MET and one or more components of the WNT pathway with a K_D of about 50 nM or less. In some embodiments, a MET-binding agent binds both MET and one or more components of the WNT pathway with a K_D of about 10 nM or less. In some embodiments, a MET-binding agent or antibody binds both MET and one or more components of the WNT pathway with a K_D of about 1 nM or less.

In some embodiments, the MET-binding agent is a bispecific agent that comprises a first binding site with a binding affinity that is weaker than the binding affinity of the second binding site. For example, in some embodiments, the bispecific agent may bind MET with a K_D ranging from about 0.1 nM to 1 nM and may bind one or more components of the WNT pathway with a K_D ranging from about 1 nM to 10 nM. Or the bispecific agent may bind MET with a K_D ranging from about 1 nM to 10 nM and may bind one or more components of the WNT pathway with a K_D ranging from about 0.1 nM to 1 nM. In some embodiments, the bispecific agent may bind one or more components of the WNT pathway with a K_D ranging from about 0.1 nM to 1 nM and may bind MET with a K_D ranging from about 1 nM to 10 nM. Or the bispecific agent may bind one or more components of the WNT pathway with a K_D ranging from about 1 nM to 10 nM and may bind MET with a K_D ranging from about 0.1 nM to 1 nM. In some embodiments, the difference in affinity between the two binding sites may be about 2-fold or more, about 3-fold or more, about 5-fold or more, about 8-fold or more, about 10-fold or more, about 15-fold or more, about 30-fold or more, about 50-fold or more, or about 100-fold or more. In some embodiments, at least one amino acid residue in at least one CDR of the antigen-binding site for MET is substituted with a different amino acid so that the affinity of the MET-binding site is altered. In some embodiments, the affinity of the MET-binding site is increased. In some embodiments, the affinity of the MET-binding site is decreased. In some embodiments, the affinities of both the MET and one or more components of the WNT pathway binding sites are altered. Modulation of the affinities of the two binding sites may affect the biological activity of the bispecific agent. For example, decreasing the affinity of the binding site for MET

or one or more components of the WNT pathway may have a desirable effect, for example decreased toxicity of the binding agent or an increased therapeutic index of the binding agent.

By way of non-limiting example, the bispecific agent may comprise (a) a first binding site that binds human MET with a K_D between about 0.1 nM and about 10 nM, and (b) a second binding site that specifically binds one or more human WNT proteins with a K_D between about 0.1 nM and about 20 nM, between about 0.5 nM and about 20 nM, between about 1.0 nM and 10 nM.

In certain embodiments, a MET-binding agent binds MET and one or more components of the WNT pathway (e.g., WNT proteins or FZD proteins) with a half maximal effective concentration (EC_{50}) of about 1 μ M or less, about 100 nM or less, about 40 nM or less, about 20 nM or less, about 10 nM or less, about 1 nM or less, or about 0.1 nM or less. In certain embodiments, a MET-binding agent binds MET and one or more components of the WNT pathway (e.g., WNT proteins or FZD proteins) with a half maximal effective concentration (EC_{50}) of about 1 μ M or less, about 100 nM or less, about 40 nM or less, about 20 nM or less, about 10 nM or less, about 1 nM or less, or about 0.1 nM or less.

In certain embodiments, the MET-binding agent comprises an antibody. In some embodiments, the antibody is a recombinant antibody. In some embodiments, the antibody is a monoclonal antibody. In some embodiments, the antibody is a chimeric antibody. In some embodiments, the antibody is a humanized antibody. In some embodiments, the antibody is a human antibody. In certain embodiments, the antibody is an IgA, IgD, IgE, IgG, or IgM antibody. In certain embodiments, the antibody is an IgG1 antibody. In certain embodiments, the antibody is an IgG2 antibody. In certain embodiments, the antibody is an antibody fragment comprising an antigen-binding site. In some embodiments, the antibody is a bispecific antibody. In some embodiments, the antibody is a monovalent antibody. In some embodiments, the antibody is a monospecific antibody. In some embodiments, the antibody is a multispecific antibody. In some embodiments, the antibody is conjugated to a cytotoxic moiety. In some embodiments, the antibody is isolated. In some embodiments, the antibody is substantially pure.

The binding agents of the present invention can be assayed for specific binding by any method known in the art. The immunoassays which can be used include, but are not limited to, competitive and non-competitive assay systems using techniques such as Biacore analysis, FACS analysis, immunofluorescence, immunocytochemistry, Western blot analysis, radioimmunoassay, ELISA, "sandwich" immunoassay, immunoprecipitation assay, precipitation reaction, gel diffusion precipitin reaction, immunodiffusion assay, agglutination assay, complement-fixation assay, immunoradiometric assay, fluorescent immunoassay, homogeneous time-resolved fluorescence assay (HTRF), and protein A immunoassay. Such assays are routine and well-known in the art (see, e.g., Ausubel et al., Editors, 1994-present, *Current Protocols in Molecular Biology*, John Wiley & Sons, Inc., New York, N.Y.).

For example, the specific binding of an agent to human MET and/or to a component of the WNT pathway (e.g., FZD proteins or WNT proteins) may be determined using ELISA. An ELISA assay comprises preparing antigen, coating wells of a 96 well microtiter plate with antigen, adding the binding agent conjugated to a detectable compound such as an enzymatic substrate (e.g. horseradish peroxidase or alkaline phosphatase) to the well, incubating for a period of time, and detecting the presence of the binding agent bound to the antigen. In some embodiments, the binding agent is not con-

jugated to a detectable compound, but instead a secondary antibody that recognizes the binding agent (e.g., an anti-Fc antibody) and is conjugated to a detectable compound is added to the well. In some embodiments, instead of coating the well with the antigen, the binding agent can be coated to the well and a secondary antibody conjugated to a detectable compound can be added following the addition of the antigen to the coated well. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the signal detected as well as other variations of ELISAs known in the art.

In another example, the specific binding of an agent to human MET and/or to a component of the WNT pathway (e.g., FZD proteins or WNT proteins) may be determined using FACS. A FACS screening assay may comprise generating a cDNA construct that expresses an antigen as a fusion protein, transfecting the construct into cells, expressing the antigen on the surface of the cells, mixing the binding agent with the transfected cells, and incubating for a period of time. The cells bound by the binding agent may be identified by using a secondary antibody conjugated to a detectable compound (e.g., PE-conjugated anti-Fc antibody) and a flow cytometer. One of skill in the art would be knowledgeable as to the parameters that can be modified to optimize the signal detected as well as other variations of FACS that may enhance screening (e.g., screening for blocking antibodies).

The binding affinity of a binding agent to an antigen (e.g., MET or a component of the WNT pathway) and the off-rate of a binding agent-target interaction can be determined by competitive binding assays. One example of a competitive binding assay is a radioimmunoassay comprising the incubation of labeled antigen/target (e.g., ^3H or ^{125}I), or fragment or variant thereof, with the binding agent of interest in the presence of increasing amounts of unlabeled antigen followed by the detection of the antibody bound to the labeled antigen/target. The affinity of the binding agent for the antigen/target and the binding off-rates can be determined from the data by Scatchard plot analysis. In some embodiments, Biacore kinetic analysis is used to determine the binding on and off rates of binding agents that bind an antigen (e.g., MET or a component of the WNT pathway). In some embodiments, Biacore kinetic analysis comprises analyzing the binding and dissociation of binding agents from chips with immobilized antigen/target (e.g., MET or a component of the WNT pathway) on their surface. In some embodiments, Biacore kinetic analysis comprises analyzing the binding and dissociation of an antigen or target (e.g., MET or a component of the WNT pathway) from chips with immobilized binding agent on their surface.

The invention provides polypeptides that specifically bind MET, bind at least one component of the WNT pathway, or bind MET and at least one component of the WNT pathway. In some embodiments, a polypeptide binds human MET. In some embodiments, a polypeptide binds one or more components of the human WNT pathway. In some embodiments, a polypeptide binds human MET and mouse MET. In some embodiments, a polypeptide binds human MET and does not bind mouse MET. In some embodiments, a polypeptide binds one or more components of the human WNT pathway. In some embodiments, a polypeptide binds one or more human FZD proteins. In some embodiments, a polypeptide binds one or more human WNT proteins. In some embodiments, a polypeptide binds human MET and does not bind mouse MET. In some embodiments, a polypeptide binds MET and one or more components of the human WNT pathway. In some embodiments, a polypeptide binds MET and one or

more human FZD proteins. In some embodiments, a polypeptide binds MET and one or more human WNT proteins.

In some embodiments, a MET-binding agent comprises a polypeptide comprising a sequence selected from the group consisting of: SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:39, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:87, and SEQ ID NO:88. In some embodiments, the MET-binding agent further comprises a polypeptide comprising a sequence selected from the group consisting of: SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, and SEQ ID NO:52.

In certain embodiments, a MET-binding agent competes for specific binding to MET with an antibody or a bispecific agent that comprises a heavy chain variable region comprising SEQ ID NO:7 and a light chain variable region comprising SEQ ID NO:8. In certain embodiments, a MET-binding agent competes with antibody 73R009 for specific binding to human MET. In certain embodiments, a MET-binding agent competes with a monovalent version of antibody 73R009 for specific binding to human MET. In some embodiments, a MET-binding agent competes with a bispecific agent comprising the heavy chain variable region and the light chain variable region of antibody 73R009 for specific binding to human MET. In some embodiments, a MET-binding agent competes for specific binding to MET with a MET-binding agent described herein in an in vitro competitive binding assay. In some embodiments, the MET is human MET. In some embodiments, the MET is mouse MET.

In certain embodiments, a MET-binding agent binds the same epitope, or essentially the same epitope, on MET as an antibody or bispecific agent of the invention. In another embodiment, a MET-binding agent is an antibody that binds an epitope on MET that overlaps with the epitope on MET bound by an antibody or bispecific agent of the invention. In certain embodiments, a MET-binding agent binds the same epitope, or essentially the same epitope, on MET as antibody 73R009. In another embodiment, the MET-binding agent is an antibody or binding agent that binds an epitope on MET that overlaps with the epitope on MET bound by antibody 73R009. In certain embodiments, a MET-binding agent binds the same epitope, or essentially the same epitope, on MET as bispecific agent 315B6. In another embodiment, the MET-binding agent is an antibody or binding agent that binds an epitope on MET that overlaps with the epitope on MET bound by bispecific agent 315B6.

In certain embodiments, the MET-binding agent is an agent that competes for specific binding to MET with the antibody 73R009 or a monovalent version of 73R009 (e.g., in a competitive binding assay). In certain embodiments, the MET-binding agent is an agent that competes for specific binding to MET with bispecific agent 315B6 (e.g., in a competitive binding assay).

In certain embodiments, a binding agent competes with bispecific agent 315B6 for specific binding to one or more WNT proteins. In some embodiments, a binding agent or antibody competes for specific binding to one or more WNT proteins with an agent described herein in an in vitro competitive binding assay. In some embodiments, the one or more WNT proteins are human WNT proteins.

In certain embodiments, a binding agent (e.g., an antibody) binds the same target, or essentially the same target, on one or more WNT proteins as a bispecific agent of the invention. In some embodiments, a binding agent binds a target on one or more WNT proteins that overlaps with the target on one or more WNT proteins bound by a bispecific agent of the inven-

tion. In certain embodiments, a binding agent binds the same target, or essentially the same target, on one or more WNT proteins as bispecific agent 315B6. In another embodiment, the binding agent binds a target on one or more WNT proteins that overlaps with the target on WNT bound by bispecific agent 315B6.

In certain embodiments, the binding agent is an agent that competes for specific binding to one or more WNT proteins with the bispecific agent 315B6 (e.g., in a competitive binding assay).

In certain embodiments, the binding agent is an agent that competes for specific binding to MET and/or one or more WNT proteins with the bispecific agent 315B6 (e.g., in a competitive binding assay).

In certain embodiments, the MET-binding agent (e.g., an antibody or bispecific agent) described herein binds MET and modulates MET activity. In some embodiments, the MET-binding agent is a MET antagonist and inhibits MET activity. MET activity may be inhibited by several different mechanisms, including but not limited to, inhibition or blockage of the MET/HGF interaction, inhibition or blockage of MET dimerization, increase in MET shedding, increase in MET internalization, and/or increase in MET degradation. In some embodiments, the MET-binding agent is a MET antagonist and inhibits tumor growth. In some embodiments, the MET-binding agent is a MET antagonist and inhibits angiogenesis. In some embodiments, the MET-binding agent is a MET antagonist and inhibits EMT.

In certain embodiments, a MET-binding agent (e.g., an antibody or bispecific agent) described herein binds one or more human WNT proteins and modulates WNT pathway activity. In some embodiments, a MET-binding agent is a WNT pathway antagonist and inhibits WNT pathway activity. In some embodiments, a MET-binding agent is a WNT pathway antagonist and inhibits β -catenin activity. In some embodiments, a MET-binding agent is a WNT pathway antagonist and inhibits tumor growth. In some embodiments, a MET-binding agent is a WNT pathway antagonist and induces differentiation of tumor cells. In some embodiments, a MET-binding agent is a WNT pathway antagonist and induces differentiation of cancer stem cells. In some embodiments, a MET-binding agent is a WNT pathway antagonist and induces expression of differentiation markers on tumor cells. In some embodiments, a MET-binding agent is a WNT pathway antagonist and induces expression of differentiation markers on cancer stem cells.

In certain embodiments, a MET-binding agent (e.g., an antibody or bispecific agent) described herein is a bispecific agent that binds human MET and modulates MET activity. In certain embodiments, a MET-binding agent described herein is a bispecific agent that binds one or more components of the human WNT pathway and modulates WNT activity. In certain embodiments, a MET-binding agent described herein is a bispecific agent that binds human MET and one or more components of the human WNT pathway and modulates both MET activity and WNT pathway activity. In some embodiments, the bispecific agent is a MET antagonist and a WNT pathway antagonist and inhibits both MET activity and WNT pathway activity. In some embodiments, the bispecific agent is a MET antagonist and a WNT pathway antagonist and inhibits MET signaling and WNT pathway signaling. In some embodiments, the bispecific agent is a MET antagonist and a WNT pathway antagonist and inhibits tumor growth.

In certain embodiments, the MET-binding agent (e.g., an antibody or a bispecific agent) is an antagonist of MET. In some embodiments, the MET-binding agent is an antagonist of MET and inhibits MET activity. In certain embodiments,

the MET-binding agent inhibits MET activity by at least about 10%, at least about 20%, at least about 30%, at least about 50%, at least about 75%, at least about 90%, or about 100%. In certain embodiments, a MET-binding agent that inhibits human MET activity comprises antibody 73R009. In certain embodiments, a MET-binding agent that inhibits human MET activity comprises a monovalent version of antibody 73R009. In certain embodiments, a MET-binding agent that inhibits human MET activity comprises the heavy chain variable region and the light chain variable region of antibody 73R009. In certain embodiments, a MET-binding agent that inhibits human MET activity is bispecific agent 315B6.

In certain embodiments, the MET-binding agent is an antagonist of the WNT pathway. In some embodiments, the MET-binding agent is an antagonist of the WNT pathway and inhibits WNT pathway activity. In certain embodiments, the MET-binding agent inhibits WNT pathway activity by at least about 10%, at least about 20%, at least about 30%, at least about 50%, at least about 75%, at least about 90%, or about 100%. In certain embodiments, a MET-binding agent that inhibits human WNT pathway activity comprises antibody 73R009. In certain embodiments, a MET-binding agent that inhibits human WNT pathway activity comprises a monovalent version of antibody 73R009. In certain embodiments, a MET-binding agent that inhibits human WNT pathway activity comprises the heavy chain variable region and the light chain variable region of antibody 73R009. In certain embodiments, a MET-binding agent that inhibits human WNT pathway activity is a bispecific agent comprising the antigen-binding site of antibody 73R009. In certain embodiments, a MET-binding agent that inhibits human WNT pathway activity is bispecific agent 315B6.

In certain embodiments, the MET-binding agent inhibits binding of MET to hepatocyte growth factor (HGF). In certain embodiments, the MET-binding agent inhibits binding of MET to HGF by at least about 10%, at least about 25%, at least about 50%, at least about 75%, at least about 90%, or at least about 95%. In certain embodiments, a MET-binding agent that inhibits binding of human MET to HGF is antibody 73R009. In certain embodiments, a MET-binding agent that inhibits binding of human MET to HGF is a monovalent version of antibody 73R009. In certain embodiments, a MET-binding agent that inhibits binding of human MET to HGF is a bispecific agent comprising the antigen-binding site of antibody 73R009. In certain embodiments, a MET-binding agent that inhibits binding of human MET to HGF is a bispecific agent comprising the heavy chain variable region and the light chain variable region of antibody 73R009. In certain embodiments, a MET-binding agent that inhibits binding of human MET to HGF is bispecific agent 315B6.

In certain embodiments, the MET-binding agent (e.g., a bispecific agent) inhibits binding of one or more WNT proteins to one or more FZD proteins. In some embodiments, the MET-binding agent (e.g., a bispecific agent) inhibits binding of one or more WNT proteins to FZD1, FZD2, FZD3, FZD4, FZD5, FZD6, FZD7, FZD8, FZD9, and/or FZD10. In some embodiments, the MET-binding agent (e.g., a bispecific agent) inhibits binding of one or more WNT proteins to FZD8. In certain embodiments, the MET-binding agent inhibits binding of one or more WNT proteins to at least one FZD receptor by at least about 10%, at least about 25%, at least about 50%, at least about 75%, at least about 90%, or at least about 95%. In certain embodiments, a MET-binding agent that inhibits binding of one or more human WNT proteins to at least one FZD receptor is bispecific agent 315B6.

In vivo and in vitro assays for determining whether a MET-binding agent (or candidate MET-binding agent) inhibits

MET activation are known in the art. For example, binding of human HGF to MET results in tyrosine phosphorylation of MET and activation of the MET signaling pathway. Therefore, human cells that are responsive to HGF may be used to assess the inhibition of HGF-induced MET activation by analyzing phosphorylation of MET and phosphorylation of downstream MET pathway components such as mitogen activate protein kinase (MAPK) and AKT. Assays to determine whether a MET-binding agent (or candidate MET-binding agent) inhibits MET dimerization, promotes MET degradation, and/or promotes MET "shedding" are also known in the art.

In vivo and in vitro assays for determining whether a MET-binding agent (or candidate MET-binding agent) inhibits WNT pathway activation or signaling are known in the art. For example, cell-based, luciferase reporter assays utilizing a TCF/Luc reporter vector containing multiple copies of the TCF-binding domain upstream of a firefly luciferase reporter gene may be used to measure β -catenin signaling levels in vitro (Gazit et al., 1999, *Oncogene*, 18: 5959-66; TOPflash, Millipore, Billerica Mass.). The level of β -catenin signaling in the presence of one or more WNT proteins (e.g., WNT(s) expressed by transfected cells or provided by WNT-conditioned media) in the presence of a binding agent is compared to the level of signaling without the binding agent present. In addition to the TCF/Luc reporter assay, the effect of a binding agent (or candidate agent) on β -catenin signaling may be measured in vitro or in vivo by measuring the effect of the agent on the level of expression of β -catenin-regulated genes, such as c-myc (He et al., 1998, *Science*, 281:1509-12), cyclin D1 (Tetsu et al., 1999, *Nature*, 398:422-6), and/or fibronectin (Gradl et al. 1999, *Mol. Cell Biol.*, 19:5576-87). In certain embodiments, the effect of a binding agent on β -catenin signaling may also be assessed by measuring the effect of the agent on the phosphorylation state of Dishevelled-1, Dishevelled-2, Dishevelled-3, LRP5, LRP6, and/or β -catenin.

In certain embodiments, the MET-binding agents have one or more of the following effects: inhibit proliferation of tumor cells, inhibit tumor growth, reduce the tumorigenicity of a tumor, reduce the frequency of cancer stem cells in a tumor, reduce the tumorigenicity of a tumor by reducing the frequency of cancer stem cells in the tumor, trigger cell death of tumor cells, induce cells in a tumor to differentiate, differentiate tumorigenic cells to a non-tumorigenic state, induce expression of differentiation markers in the tumor cells, prevent metastasis of tumor cells, inhibit angiogenesis, decrease survival of tumor cells, or any combination of the above.

In certain embodiments, the MET-binding agents are capable of inhibiting tumor growth. In certain embodiments, the MET-binding agents are capable of inhibiting tumor growth in vivo (e.g., in a xenograft mouse model, and/or in a human having cancer). In certain embodiments, tumor growth is inhibited at least about two-fold, about three-fold, about five-fold, about ten-fold, about 50-fold, about 100-fold, or about 1000-fold as compared to an untreated tumor.

In certain embodiments, the MET-binding agents are capable of reducing the tumorigenicity of a tumor. In certain embodiments, the MET-binding agent is capable of reducing the tumorigenicity of a tumor comprising cancer stem cells in an animal model, such as a mouse xenograft model. In certain embodiments, the MET-binding agent is capable of reducing the tumorigenicity of a tumor by decreasing the number or frequency of cancer stem cells in the tumor. In certain embodiments, the number or frequency of cancer stem cells in a tumor is reduced by at least about two-fold, about three-fold, about five-fold, about ten-fold, about 50-fold, about 100-fold, or about 1000-fold. In certain embodiments, the

reduction in the number or frequency of cancer stem cells is determined by limiting dilution assay using an animal model. Additional examples and guidance regarding the use of limiting dilution assays to determine a reduction in the number or frequency of cancer stem cells in a tumor can be found, e.g., in International Publication Number WO 2008/042236; U.S. Patent Publication No. 2008/0064049; and U.S. Patent Publication No. 2008/0178305.

In certain embodiments, the MET-binding agents described herein have a circulating half-life in mice, cynomolgus monkeys, or humans of at least about 2 hours, at least about 5 hours, at least about 10 hours, at least about 24 hours, at least about 3 days, at least about 1 week, or at least about 2 weeks. In certain embodiments, the MET-binding agent is an IgG (e.g., IgG1 or IgG2) antibody that has a circulating half-life in mice, cynomolgus monkeys, or humans of at least about 2 hours, at least about 5 hours, at least about 10 hours, at least about 24 hours, at least about 3 days, at least about 1 week, or at least about 2 weeks. In certain embodiments, the MET-binding agent is an agent comprising at least one IgG (e.g., IgG1 or IgG2) constant region that has a circulating half-life in mice, cynomolgus monkeys, or humans of at least about 2 hours, at least about 5 hours, at least about 10 hours, at least about 24 hours, at least about 3 days, at least about 1 week, or at least about 2 weeks. Methods of increasing (or decreasing) the half-life of agents such as polypeptides, soluble receptors, and/or antibodies are known in the art. For example, known methods of increasing the circulating half-life of IgG antibodies include the introduction of mutations in the Fc region which increase the pH-dependent binding of the antibody to the neonatal Fc receptor (FcRn) at pH 6.0 (see, e.g., U.S. Patent Publication Nos. 2005/0276799, 2007/0148164, and 2007/0122403). Known methods of increasing the circulating half-life of antibody fragments lacking the Fc region include such techniques as PEGylation.

In some embodiments, the binding agents described herein are antibodies. Polyclonal antibodies can be prepared by any known method. In some embodiments, polyclonal antibodies are produced by immunizing an animal (e.g., a rabbit, rat, mouse, goat, or donkey) with an antigen of interest (e.g., a purified peptide fragment, full-length recombinant protein, or fusion protein) by multiple subcutaneous or intraperitoneal injections. The antigen can be optionally conjugated to a carrier such as keyhole limpet hemocyanin (KLH) or serum albumin. The antigen (with or without a carrier protein) is diluted in sterile saline and usually combined with an adjuvant (e.g., Complete or Incomplete Freund's Adjuvant) to form a stable emulsion. After a sufficient period of time, polyclonal antibodies are recovered from the immunized animal, usually from blood or ascites. The polyclonal antibodies can be purified from serum or ascites according to standard methods in the art including, but not limited to, affinity chromatography, ion-exchange chromatography, gel electrophoresis, and dialysis.

In some embodiments, the binding agents are monoclonal antibodies. Monoclonal antibodies can be prepared using hybridoma methods known to one of skill in the art (see e.g., Kohler and Milstein, 1975, *Nature*, 256:495-497). In some embodiments, using the hybridoma method, a mouse, hamster, or other appropriate host animal, is immunized as described above to elicit from lymphocytes the production of antibodies that specifically bind the immunizing antigen. In some embodiments, lymphocytes can be immunized in vitro. In some embodiments, the immunizing antigen can be a human protein or a portion thereof. In some embodiments, the immunizing antigen can be a mouse protein or a portion thereof.

Following immunization, lymphocytes are isolated and fused with a suitable myeloma cell line using, for example, polyethylene glycol. The hybridoma cells are selected using specialized media as known in the art and unfused lymphocytes and myeloma cells do not survive the selection process. Hybridomas that produce monoclonal antibodies directed specifically against a chosen antigen may be identified by a variety of methods including, but not limited to, immunoprecipitation, immunoblotting, and in vitro binding assays (e.g., flow cytometry, FACS, ELISA, and radioimmunoassay). The hybridomas can be propagated either in vitro culture using standard methods (J. W. Goding, 1996, *Monoclonal Antibodies: Principles and Practice*, 3rd Edition, Academic Press, San Diego, Calif.) or in vivo as ascites tumors in an animal. The monoclonal antibodies can be purified from the culture medium or ascites fluid according to standard methods in the art including, but not limited to, affinity chromatography, ion-exchange chromatography, gel electrophoresis, and dialysis.

In certain embodiments, monoclonal antibodies can be made using recombinant DNA techniques as known to one skilled in the art. The polynucleotides encoding a monoclonal antibody are isolated from mature B-cells or hybridoma cells, such as by RT-PCR using oligonucleotide primers that specifically amplify the genes encoding the heavy and light chains of the antibody, and their sequence is determined using standard techniques. The isolated polynucleotides encoding the heavy and light chains are then cloned into suitable expression vectors which produce the monoclonal antibodies when transfected into host cells such as *E. coli*, simian COS cells, Chinese hamster ovary (CHO) cells, or myeloma cells that do not otherwise produce immunoglobulin proteins.

In certain other embodiments, recombinant monoclonal antibodies, or fragments thereof, can be isolated from phage display libraries expressing variable domains or CDRs of a desired species (see e.g., McCafferty et al., 1990, *Nature*, 348:552-554; Clackson et al., 1991, *Nature*, 352:624-628; and Marks et al., 1991, *J. Mol. Biol.*, 222:581-597). In some embodiments, recombinant monoclonal antibodies, or fragments thereof, can be isolated from mammalian cell display libraries expressing variable domains or CDRs of a desired species (see e.g., U.S. patent publication No. 2011/0287979).

The polynucleotide(s) encoding a monoclonal antibody can be modified, for example, by using recombinant DNA technology to generate alternative antibodies or alternative bispecific agents. In some embodiments, the constant domains of the light and heavy chains of, for example, a mouse monoclonal antibody can be substituted for those regions of, for example, a human antibody to generate a chimeric antibody, or for a non-immunoglobulin polypeptide to generate a fusion antibody. In some embodiments, the constant regions are truncated or removed to generate the desired antibody fragment of a monoclonal antibody. Site-directed or high-density mutagenesis of the variable region can be used to optimize specificity, affinity, etc. of a monoclonal antibody.

In some embodiments, the binding agent is a humanized antibody. Typically, humanized antibodies are human immunoglobulins in which residues from the CDRs are replaced by residues from a CDR of a non-human species (e.g., mouse, rat, rabbit, hamster, etc.) that have the desired specificity, affinity, and/or binding capability using methods known to one skilled in the art. In some embodiments, the Fv framework region residues of a human immunoglobulin are replaced with the corresponding residues in an antibody from a non-human species that has the desired specificity, affinity, and/or binding capability. In some embodiments, a human-

ized antibody can be further modified by the substitution of additional residues either in the Fv framework region and/or within the replaced non-human residues to refine and optimize antibody specificity, affinity, and/or capability. In general, a humanized antibody will comprise substantially all of at least one, and typically two or three, variable domain regions containing all, or substantially all, of the CDRs that correspond to the non-human immunoglobulin whereas all, or substantially all, of the framework regions are those of a human immunoglobulin consensus sequence. In some embodiments, a humanized antibody can also comprise at least a portion of an immunoglobulin constant region or domain (Fc), typically that of a human immunoglobulin. In certain embodiments, such humanized antibodies are used therapeutically because they may reduce antigenicity and HAMA (human anti-mouse antibody) responses when administered to a human subject. One skilled in the art would be able to obtain a functional humanized antibody with reduced immunogenicity following known techniques (see e.g., U.S. Pat. Nos. 5,225,539; 5,585,089; 5,693,761; and 5,693,762).

In certain embodiments, the binding agent is a human antibody. Human antibodies can be directly prepared using various techniques known in the art. In some embodiments, human antibodies may be generated from immortalized human B lymphocytes immunized in vitro or from lymphocytes isolated from an immunized individual. In either case, cells that produce an antibody directed against a target antigen can be generated and isolated (see, e.g., Cole et al., 1985, *Monoclonal Antibodies and Cancer Therapy*, Alan R. Liss, p. 77; Boerner et al., 1991, *J. Immunol.*, 147:86-95; and U.S. Pat. Nos. 5,750,373; 5,567,610; and 5,229,275). In some embodiments, the human antibody can be selected from a phage library, where that phage library expresses human antibodies (Vaughan et al., 1996, *Nature Biotechnology*, 14:309-314; Sheets et al., 1998, *PNAS*, 95:6157-6162; Hoogenboom and Winter, 1991, *J. Mol. Biol.*, 227:381; Marks et al., 1991, *J. Mol. Biol.*, 222:581). Alternatively, phage display technology can be used to produce human antibodies and antibody fragments in vitro, from immunoglobulin variable domain gene repertoires from unimmunized donors. Techniques for the generation and use of antibody phage libraries are also described in U.S. Pat. Nos. 5,969,108; 6,172,197; 5,885,793; 6,521,404; 6,544,731; 6,555,313; 6,582,915; 6,593,081; 6,300,064; 6,653,068; 6,706,484; and 7,264,963; and Rothe et al., 2008, *J. Mol. Bio.*, 376:1182-1200. Once antibodies are identified, affinity maturation strategies known in the art, including but not limited to, chain shuffling (Marks et al., 1992, *Bio/Technology*, 10:779-783) and site-directed mutagenesis, may be employed to generate high affinity human antibodies.

In some embodiments, human antibodies can be made in transgenic mice that contain human immunoglobulin loci. Upon immunization these mice are capable of producing the full repertoire of human antibodies in the absence of endogenous immunoglobulin production. This approach is described in U.S. Pat. Nos. 5,545,807; 5,545,806; 5,569,825; 5,625,126; 5,633,425; and 5,661,016.

This invention also encompasses bispecific agents and bispecific antibodies. Bispecific agents are capable of specifically recognizing and binding at least two different targets or epitopes. The different targets can either be within the same molecule (e.g., two targets on a single protein) or on different molecules (e.g., one target on a protein and a second target on a second protein). In some embodiments, a bispecific agent or bispecific antibody has enhanced potency as compared to an individual agent or antibody or to a mixture of two agents. In

some embodiments, a bispecific agent or bispecific antibody has reduced toxicity as compared to an individual agent or to a combination of more than one agent. It is known to those of skill in the art that any binding agent may have unique pharmacokinetics (PK) (e.g., circulating half-life). In some embodiments, a bispecific agent or bispecific antibody has the ability to synchronize the PK of two active binding agents wherein the two individual binding agents have different PK profiles. In some embodiments, a bispecific agent or bispecific antibody has the ability to concentrate the actions of two binding agents in a common area (e.g., a tumor and/or tumor environment). In some embodiments, a bispecific agent or bispecific antibody has the ability to concentrate the actions of two binding agents to a common target (e.g., a tumor or a tumor cell). In some embodiments, a bispecific agent or bispecific antibody has the ability to target the actions of two binding agents to more than one biological pathway or function.

In certain embodiments, a bispecific antibody specifically binds MET and a second target. In certain embodiments, a bispecific antibody specifically binds MET and one or more components of the WNT pathway. In some embodiments, a bispecific antibody specifically binds human MET and one or more human WNT proteins. In some embodiments, a bispecific antibody specifically binds human MET and one or more human FZD proteins. In some embodiments, the bispecific antibody is a monoclonal human. In some embodiments, the bispecific antibody is a humanized antibody. In some embodiments, the bispecific antibody is a human antibody. In some embodiments, the bispecific antibody is a chimeric antibody. In some embodiments, the bispecific antibody reduces cancer stem cell number or frequency. In some embodiments, the bispecific antibody has decreased toxicity and/or side effects. In some embodiments, the bispecific antibody has decreased toxicity and/or side effects as compared to a mixture of the two individual antibodies or the antibodies as single agents. In some embodiments, the bispecific antibody has an increased therapeutic index. In some embodiments, the bispecific antibody has an increased therapeutic index as compared to a mixture of the two individual antibodies or the antibodies as single agents.

In some embodiments, a bispecific antibody can specifically recognize and bind human MET as well as a second antigen target, such as an effector molecule on a leukocyte (e.g., CD2, CD3, CD28, CD80, or CD86) or a Fc receptor (e.g., CD64, CD32, or CD16) so as to focus cellular defense mechanisms to the cell expressing MET. In some embodiments, a bispecific antibody can be used to direct cytotoxic agents to cells which express a particular target antigen. These antibodies possess an antigen-binding site (e.g., to human MET) and a second site which binds a cytotoxic agent or a radionuclide chelator, such as EOTUBE, DPTA, DOTA, or TETA.

Techniques for making bispecific antibodies are known by those skilled in the art, see for example, Millstein et al., 1983, *Nature*, 305:537-539; Brennan et al., 1985, *Science*, 229:81; Suresh et al., 1986, *Methods in Enzymol.*, 121:120; Traun-ecker et al., 1991, *EMBO J.*, 10:3655-3659; Shalaby et al., 1992, *J. Exp. Med.*, 175:217-225; Kostelny et al., 1992, *J. Immunol.*, 148:1547-1553; Gruber et al., 1994, *J. Immunol.*, 152:5368; U.S. Pat. No. 5,731,168; International Publication No. WO 2009/089004; and U.S. Patent Publication No. 2011/0123532. In some embodiments, the bispecific antibodies comprise heavy chain constant regions with modifications in the amino acids which are part of the interface between the two heavy chains. In some embodiments, the bispecific antibodies can be generated using a “knobs-into-holes” strategy

(see, e.g., U.S. Pat. No. 5,731,168; Ridgway et al. 1996, *Prot. Engin.*, 9:617-621). At times the “knobs” and “holes” terminology is replaced with the terms “protuberances” and “cavities”. In some embodiments, the bispecific antibodies may comprise variant hinge regions incapable of forming disulfide linkages between the heavy chains (see, e.g., WO 2006/028936). In some embodiments, the modifications may comprise changes in amino acids that result in altered electrostatic interactions. In some embodiments, the modifications may comprise changes in amino acids that result in altered hydrophobic/hydrophilic interactions.

Bispecific antibodies can be intact antibodies or antibody fragments comprising antigen-binding sites. Antibodies with more than two valencies are also contemplated. For example, trispecific antibodies can be prepared (Tutt et al., 1991, *J. Immunol.*, 147:60). Thus, in certain embodiments the antibodies to MET and/or one or more components of the WNT pathway are multispecific.

In certain embodiments, the antibodies (or other polypeptides) described herein may be monospecific. In certain embodiments, each of the one or more antigen-binding sites that an antibody contains is capable of binding (or binds) a homologous epitope on different proteins.

In certain embodiments, the binding agent comprises an antibody fragment. Antibody fragments may have different functions or capabilities than intact antibodies; for example, antibody fragments can have increased tumor penetration. Various techniques are known for the production of antibody fragments including, but not limited to, proteolytic digestion of intact antibodies. In some embodiments, antibody fragments include a F(ab')₂ fragment produced by pepsin digestion of an antibody molecule. In some embodiments, antibody fragments include a Fab fragment generated by reducing the disulfide bridges of an F(ab')₂ fragment. In other embodiments, antibody fragments include a Fab fragment generated by the treatment of the antibody molecule with papain and a reducing agent. In certain embodiments, antibody fragments are produced using recombinant techniques. In some embodiments, antibody fragments include Fv or single chain Fv (scFv) fragments. Fab, Fv, and scFv antibody fragments can be expressed in and secreted from *E. coli* or other host cells, allowing for the production of large amounts of these fragments. In some embodiments, antibody fragments are isolated from antibody phage libraries as discussed herein. For example, methods can be used for the construction of Fab expression libraries (Huse et al., 1989, *Science*, 246:1275-1281) to allow rapid and effective identification of monoclonal Fab fragments with the desired specificity for MET and/or one or more components of the WNT pathway or derivatives, fragments, analogs or homologs thereof. In some embodiments, antibody fragments are linear antibody fragments. In certain embodiments, antibody fragments are monospecific or bispecific. In certain embodiments, the binding agent is a scFv. Various techniques can be used for the production of single-chain antibodies specific to MET or one or more components of the WNT pathway.

It can further be desirable, especially in the case of antibody fragments, to modify an antibody in order to alter (e.g., increase or decrease) its serum half-life. This can be achieved, for example, by incorporation of a salvage receptor binding epitope into the antibody fragment by mutation of the appropriate region in the antibody fragment or by incorporating the epitope into a peptide tag that is then fused to the antibody fragment at either end or in the middle (e.g., by DNA or peptide synthesis).

Heteroconjugate antibodies are also within the scope of the present invention. Heteroconjugate antibodies are composed

of two covalently joined antibodies. Such antibodies have, for example, been proposed to target immune cells to unwanted cells (see, e.g., U.S. Pat. No. 4,676,980). It is also contemplated that the heteroconjugate antibodies can be prepared in vitro using known methods in synthetic protein chemistry, including those involving crosslinking agents. For example, immunotoxins can be constructed using a disulfide exchange reaction or by forming a thioether bond. Examples of suitable reagents for this purpose include iminothiolate and methyl-4-mercaptobutyrimidate.

For the purposes of the present invention, it should be appreciated that modified agents can comprise any type of region that provides for the association of the agent with the target (i.e., human MET or a human WNT protein). In some embodiments, the region is a variable region that may comprise or be derived from any type of mammal that can be induced to mount a humoral response and generate immunoglobulins against the desired antigen. As such, a variable region of modified antibodies can be, for example, of human, murine, non-human primate (e.g. cynomolgus monkeys, macaques, etc.) or rabbit origin. In some embodiments, both a variable and a constant region of a modified immunoglobulin are human. In other embodiments, variable regions of compatible antibodies (usually derived from a non-human source) can be engineered or specifically tailored to improve the binding properties or reduce the immunogenicity of the molecule. In this respect, variable regions useful in the present invention can be humanized or otherwise altered through the inclusion of imported amino acid sequences.

In certain embodiments, variable domains in both the heavy and light chains are altered by at least partial replacement of one or more CDRs and, if necessary, by partial framework region replacement and sequence modification and/or alteration. Although the CDRs may be derived from an antibody of the same class or even subclass as the antibody from which the framework regions are derived, it is envisaged that the CDRs may be derived from an antibody of different class and often from an antibody from a different species. It may not be necessary to replace all of the CDRs with all of the CDRs from the donor variable region to transfer the antigen binding capacity of one variable domain to another. Rather, it may only be necessary to transfer those residues that are required to maintain the activity of the antigen-binding site.

Alterations to a variable region notwithstanding, those skilled in the art will appreciate that the modified antibodies of this invention will comprise antibodies (e.g., full-length antibodies or immunoreactive fragments thereof) or bispecific agents in which at least a fraction of one or more of the constant region domains has been deleted or otherwise altered so as to provide desired biochemical characteristics such as increased tumor localization or increased serum half-life when compared with an antibody of approximately the same immunogenicity comprising a native or unaltered constant region. In some embodiments, the constant region of the modified antibodies will comprise a human constant region. Modifications to the constant region compatible with this invention comprise additions, deletions or substitutions of one or more amino acids in one or more domains. The modified antibodies and/or bispecific agents disclosed herein may comprise alterations or modifications to one or more of the three heavy chain constant domains (CH1, CH2 or CH3) and/or to the light chain constant domain (CL). In some embodiments, one or more domains are partially or entirely deleted from the constant regions of the modified antibodies. In some embodiments, the modified antibodies will comprise domain deleted constructs or variants wherein the entire CH2 domain has been removed (Δ CH2 constructs). In some

embodiments, the omitted constant region domain is replaced by a short amino acid spacer (e.g., 10 amino acid residues) that provides some of the molecular flexibility typically imparted by the absent constant region.

In some embodiments, the modified antibodies or bispecific agents are engineered to fuse the CH3 domain directly to the hinge region of the antibody. In other embodiments, a peptide spacer is inserted between the hinge region and the modified CH2 and/or CH3 domains. For example, constructs may be expressed wherein the CH2 domain has been deleted and the remaining CH3 domain (modified or unmodified) is joined to the hinge region with a 5-20 amino acid spacer. Such a spacer may be added to ensure that the regulatory elements of the constant domain remain free and accessible or that the hinge region remains flexible. However, it should be noted that amino acid spacers may, in some cases, prove to be immunogenic and elicit an unwanted immune response against the construct. Accordingly, in certain embodiments, any spacer added to the construct will be relatively non-immunogenic so as to maintain the desired biological qualities of the modified antibodies.

In some embodiments, the modified antibodies or bispecific agents may have only a partial deletion of a constant domain or substitution of a few or even a single amino acid. For example, the mutation of a single amino acid in selected areas of the CH2 domain may be enough to substantially reduce Fc binding and thereby increase cancer cell localization and/or tumor penetration. Similarly, it may be desirable to simply delete the part of one or more constant region domains that control a specific effector function (e.g. complement C1q binding) to be modulated. Such partial deletions of the constant regions may improve selected characteristics of the antibody (serum half-life) while leaving other desirable functions associated with the subject constant region domain intact. Moreover, as alluded to above, the constant regions of the disclosed antibodies and/or bispecific agents may be modified through the mutation or substitution of one or more amino acids that enhances the profile of the resulting construct. In this respect it may be possible to disrupt the activity provided by a conserved binding site (e.g., Fc binding) while substantially maintaining the configuration and immunogenic profile of the modified antibody. In certain embodiments, the modified antibodies and/or bispecific agents comprise the addition of one or more amino acids to the constant region to enhance desirable characteristics such as decreasing or increasing effector function or provide for more cytotoxin or carbohydrate attachment sites.

It is known in the art that the constant region mediates several effector functions. For example, binding of the C1 component of complement to the Fc region of IgG or IgM antibodies (bound to antigen) activates the complement system. Activation of complement is important in the opsonization and lysis of cell pathogens. The activation of complement also stimulates the inflammatory response and can also be involved in autoimmune hypersensitivity. In addition, the Fc region of an antibody or a Fc-fusion proteins can bind a cell expressing a Fc receptor (FcR). There are a number of Fc receptors which are specific for different classes of antibody, including IgG (gamma receptors), IgE (epsilon receptors), IgA (alpha receptors) and IgM (mu receptors). Binding of antibody to Fc receptors on cell surfaces triggers a number of important and diverse biological responses including engulfment and destruction of antibody-coated particles, clearance of immune complexes, lysis of antibody-coated target cells by killer cells (called antibody-dependent cell cytotoxicity or ADCC), release of inflammatory mediators, placental transfer, and control of immunoglobulin production.

In certain embodiments, the modified antibodies and/or bispecific agents provide for altered effector functions that, in turn, affect the biological profile of the administered antibody. For example, in some embodiments, the deletion or inactivation (through point mutations or other means) of a constant region domain may reduce Fc receptor binding of the circulating modified antibody thereby increasing cancer cell localization and/or tumor penetration. In other embodiments, the constant region modifications increase the serum half-life of the antibody and/or bispecific agent. In other embodiments, the constant region modifications reduce the serum half-life of the antibody and/or bispecific agent. In some embodiments, the constant region is modified to eliminate disulfide linkages or oligosaccharide moieties. Modifications to the constant region in accordance with this invention may easily be made using well known biochemical or molecular engineering techniques known to those of skill in the art.

In certain embodiments, an antibody and/or bispecific agent does not have one or more effector functions. For instance, in some embodiments, the antibody or bispecific agent has no ADCC activity, and/or no complement-dependent cytotoxicity (CDC) activity. In certain embodiments, the antibody and/or bispecific agent does not bind an Fc receptor, and/or complement factors. In certain embodiments, the antibody and/or bispecific agent has no effector function.

The present invention further embraces variants and equivalents which are substantially homologous to the chimeric, humanized, and human antibodies, or antibody fragments thereof, or bispecific agents, described herein. These can contain, for example, conservative substitution mutations, i.e. the substitution of one or more amino acids by similar amino acids. For example, conservative substitution refers to the substitution of an amino acid with another amino acid within the same general class such as, for example, one acidic amino acid with another acidic amino acid, one basic amino acid with another basic amino acid or one neutral amino acid by another neutral amino acid. What is intended by a conservative amino acid substitution is well known in the art and described herein.

Thus, the present invention provides methods for producing an antibody or bispecific agent that binds MET and/or one or more components of the WNT pathway, including bispecific agents that specifically bind both MET and one or more WNT proteins. In some embodiments, the method for producing an antibody that binds MET or one or more components of the WNT pathway comprises using hybridoma techniques. In some embodiments, the method of generating an agent that binds MET or one or more components of the WNT pathway or a bispecific agent that binds MET and one or more components of the WNT pathway comprises screening a human phage display library. In some embodiments, the method of generating an agent that binds MET or one or more components of the WNT pathway or a bispecific agent that binds MET and one or more components of the WNT pathway comprises screening a mammalian cell display library. The present invention further provides methods of identifying an agent that binds MET and/or one or more components of the WNT pathway. In some embodiments, the agent is identified by FACS screening for binding to MET or a fragment thereof. In some embodiments, the agent is identified by FACS screening for binding to one or more components of the WNT pathway or a fragment thereof. In some embodiments, the agent is identified by FACS screening for binding to both MET and one or more components of the WNT pathway or a fragment thereof. In some embodiments, the agent is identified by screening using ELISA for binding to MET. In some embodiments, the agent is identified by screening using

ELISA for binding to one or more components of the WNT pathway. In some embodiments, the agent is identified by screening using ELISA for binding to MET and one or more components of the WNT pathway. In some embodiments, the agent is identified by FACS screening for blocking of binding of human MET to human hepatocyte growth factor. In some embodiments, the agent is identified by FACS screening for blocking of binding of one or more WNT proteins to a human FZD protein. In some embodiments, the agent is identified by screening for inhibition or blocking of WNT pathway signaling. In some embodiments, the agent is identified by screening for inhibition or blocking of MET activity.

In certain embodiments, the antibodies and/or bispecific agents described herein are isolated. In certain embodiments, the antibodies and/or bispecific agents described herein are substantially pure.

In some embodiments of the present invention, the MET-binding agents are polypeptides. The polypeptides can be recombinant polypeptides, natural polypeptides, or synthetic polypeptides comprising an antibody, or fragment thereof, that bind MET and/or one or more components of the WNT pathway. The polypeptides can be recombinant polypeptides, natural polypeptides, or synthetic polypeptides comprising a soluble receptor, or fragment thereof, that bind one or more components of the WNT pathway. It will be recognized in the art that some amino acid sequences of the binding agents described herein can be varied without significant effect on the structure or function of the protein. Thus, the invention further includes variations of the polypeptides which show substantial activity or which include regions of an antibody, or fragment thereof, against human MET and/or one or more components of the WNT pathway. In some embodiments, amino acid sequence variations of MET-binding polypeptides include deletions, insertions, inversions, repeats, and/or other types of substitutions.

In some embodiments, the polypeptides described herein are isolated. In some embodiments, the polypeptides described herein are substantially pure.

The polypeptides, analogs and variants thereof, can be further modified to contain additional chemical moieties not normally part of the polypeptide. The derivatized moieties can improve or otherwise modulate the solubility, the biological half-life, and/or absorption of the polypeptide. The moieties can also reduce or eliminate undesirable side effects of the polypeptides and variants. An overview for chemical moieties can be found in *Remington: The Science and Practice of Pharmacy*, 22nd Edition, 2012, Pharmaceutical Press, London.

The polypeptides described herein can be produced by any suitable method known in the art. Such methods range from direct protein synthesis methods to constructing a DNA sequence encoding polypeptide sequences and expressing those sequences in a suitable host. In some embodiments, a DNA sequence is constructed using recombinant technology by isolating or synthesizing a DNA sequence encoding a wild-type protein of interest. Optionally, the sequence can be mutagenized by site-specific mutagenesis to provide functional analogs thereof. See, e.g., Zoeller et al., 1984, *PNAS*, 81:5662-5066 and U.S. Pat. No. 4,588,585.

In some embodiments, a DNA sequence encoding a polypeptide of interest may be constructed by chemical synthesis using an oligonucleotide synthesizer. Oligonucleotides can be designed based on the amino acid sequence of the desired polypeptide and selecting those codons that are favored in the host cell in which the recombinant polypeptide of interest will be produced. Standard methods can be applied to synthesize a polynucleotide sequence encoding an isolated

polypeptide of interest. For example, a complete amino acid sequence can be used to construct a back-translated gene. Further, a DNA oligomer containing a nucleotide sequence coding for the particular isolated polypeptide can be synthesized. For example, several small oligonucleotides coding for portions of the desired polypeptide can be synthesized and then ligated. The individual oligonucleotides typically contain 5' or 3' overhangs for complementary assembly.

Once assembled (by synthesis, site-directed mutagenesis, or another method), the polynucleotide sequences encoding a particular polypeptide of interest can be inserted into an expression vector and operatively linked to an expression control sequence appropriate for expression of the protein in a desired host. Proper assembly can be confirmed by nucleotide sequencing, restriction enzyme mapping, and/or expression of a biologically active polypeptide in a suitable host. As is well-known in the art, in order to obtain high expression levels of a transfected gene in a host, the gene must be operatively linked to transcriptional and translational expression control sequences that are functional in the chosen expression host.

In certain embodiments, recombinant expression vectors are used to amplify and express DNA encoding antibodies or fragments thereof or bispecific agents that bind human MET and/or one or more components of the WNT pathway. For example, recombinant expression vectors can be replicable DNA constructs which have synthetic or cDNA-derived DNA fragments encoding a polypeptide chain of a MET-binding agent, such as an anti-MET antibody or bispecific agent comprising an anti-MET antibody and a FZD soluble receptor, or fragment thereof, operatively linked to suitable transcriptional and/or translational regulatory elements derived from mammalian, microbial, viral, or insect genes. A transcriptional unit generally comprises an assembly of (1) a genetic element or elements having a regulatory role in gene expression, for example, transcriptional promoters or enhancers, (2) a structural or coding sequence which is transcribed into mRNA and translated into protein, and (3) appropriate transcription and translation initiation and termination sequences. Regulatory elements can include an operator sequence to control transcription. The ability to replicate in a host, usually conferred by an origin of replication, and a selection gene to facilitate recognition of transformants can additionally be incorporated. DNA regions are "operatively linked" when they are functionally related to each other. For example, DNA for a signal peptide (secretory leader) is operatively linked to DNA for a polypeptide if it is expressed as a precursor which participates in the secretion of the polypeptide; a promoter is operatively linked to a coding sequence if it controls the transcription of the sequence; or a ribosome binding site is operatively linked to a coding sequence if it is positioned so as to permit translation. In some embodiments, structural elements intended for use in yeast expression systems include a leader sequence enabling extracellular secretion of translated protein by a host cell. In other embodiments, in situations where recombinant protein is expressed without a leader or transport sequence, it can include an N-terminal methionine residue. This residue can optionally be subsequently cleaved from the expressed recombinant protein to provide a final product.

The choice of an expression control sequence and an expression vector depends upon the choice of host. A wide variety of expression host/vector combinations can be employed. Useful expression vectors for eukaryotic hosts include, for example, vectors comprising expression control sequences from SV40, bovine papilloma virus, adenovirus, and cytomegalovirus. Useful expression vectors for bacterial

hosts include known bacterial plasmids, such as plasmids from *E. coli*, including pCR1, pBR322, pMB9, and their derivatives, and wider host range plasmids, such as M13 and other filamentous single-stranded DNA phages.

The binding agents (e.g., polypeptides) of the present invention can be expressed from one or more vectors. For example, in some embodiments, a heavy chain polypeptide is expressed by one vector and a light chain polypeptide is expressed by a second vector. In some embodiments, a heavy chain polypeptide and a light chain polypeptide are expressed by one vector. In some embodiments, a heavy chain polypeptide is expressed by one vector, a light chain polypeptide is expressed by a second vector and a polypeptide comprising a soluble receptor is expressed by a third vector. In some embodiments, a heavy chain polypeptide and a light chain polypeptide are expressed by one vector and a polypeptide comprising a soluble receptor is expressed by a second vector. In some embodiments, three polypeptides are expressed from one vector. Thus, in some embodiments, a heavy chain polypeptide, a light chain polypeptide, and a polypeptide comprising a soluble receptor are expressed by a single vector.

Suitable host cells for expression of a MET-binding polypeptide or agent (or a MET, WNT, or FZD protein to use as an antigen) include prokaryotes, yeast cells, insect cells, or higher eukaryotic cells under the control of appropriate promoters. Prokaryotes include gram-negative or gram-positive organisms, for example *E. coli* or *Bacillus*. Higher eukaryotic cells include established cell lines of mammalian origin as described below. Cell-free translation systems may also be employed. Appropriate cloning and expression vectors for use with bacterial, fungal, yeast, and mammalian cellular hosts are described in Pouwels et al., 1985, *Cloning Vectors: A Laboratory Manual*, Elsevier, New York, N.Y. Additional information regarding methods of protein production, including antibody production, can be found, e.g., in U.S. Patent Publication No. 2008/0187954; U.S. Pat. Nos. 6,413,746; 6,660,501; and International Patent Publication No. WO 04/009823.

Various mammalian cell culture systems may be used to express recombinant polypeptides. Expression of recombinant proteins in mammalian cells may be desirable because these proteins are generally correctly folded, appropriately modified, and biologically functional. Examples of suitable mammalian host cell lines include, but are not limited to, COS-7 (monkey kidney-derived), L-929 (murine fibroblast-derived), C127 (murine mammary tumor-derived), 3T3 (murine fibroblast-derived), CHO (Chinese hamster ovary-derived), HeLa (human cervical cancer-derived), BHK (hamster kidney fibroblast-derived), HEK-293 (human embryonic kidney-derived) cell lines and variants of these cell lines. Mammalian expression vectors can comprise non-transcribed elements such as an origin of replication, a suitable promoter and enhancer linked to the gene to be expressed, and other 5' or 3' flanking non-transcribed sequences, and 5' or 3' non-translated sequences, such as necessary ribosome binding sites, a polyadenylation site, splice donor and acceptor sites, and transcriptional termination sequences.

Expression of recombinant proteins in insect cell culture systems (e.g., baculovirus) also offers a robust method for producing correctly folded and biologically functional proteins. Baculovirus systems for production of heterologous proteins in insect cells are well-known to those of skill in the art (see, e.g., Luckow and Summers, 1988, *Bio/Technology*, 6:47).

Thus, the present invention provides cells comprising the binding agents described herein. In some embodiments, the cells produce the binding agents described herein. In certain embodiments, the cells produce an antibody. In some embodiments, the cells produce a MET-binding agent, such as an anti-MET antibody. In some embodiments, the cells produce a bispecific agent that binds MET. In some embodiments, the cells produce a bispecific agent that binds MET and one or more components of the WNT pathway. In some embodiments, the cells produce a bispecific agent that binds MET and one or more FZD proteins. In some embodiments, the cells produce a bispecific agent that binds MET and one or more WNT proteins. In certain embodiments, the cells produce antibody 73R009. In certain embodiments, the cells produce a bispecific agent which comprises an antigen-binding site from antibody 73R009. In certain embodiments, the cells produce a bispecific agent which comprises an antigen-binding site from antibody 73R009 and a FZD Fri domain. In certain embodiments, the cells produce a bispecific agent which comprises an antigen-binding site from antibody 73R009 and a FZD8 Fri domain. In certain embodiments, the cells produce the bispecific agent 315B6.

The proteins produced by a transformed host can be purified according to any suitable method. Standard methods include chromatography (e.g., ion exchange, affinity, and sizing column chromatography), centrifugation, differential solubility, or by any other standard technique for protein purification. Affinity tags such as hexa-histidine, maltose binding domain, influenza coat sequence, and glutathione-S-transferase can be attached to the protein to allow easy purification by passage over an appropriate affinity column. Affinity chromatography used for purifying immunoglobulins can include Protein A, Protein G, and Protein L chromatography. Isolated proteins can be physically characterized using such techniques as proteolysis, size exclusion chromatography (SEC), mass spectrometry (MS), nuclear magnetic resonance (NMR), isoelectric focusing (IEF), high performance liquid chromatography (HPLC), and x-ray crystallography. The purity of isolated proteins can be determined using techniques known to those of skill in the art, including but not limited to, SDS-PAGE, SEC, capillary gel electrophoresis, IEF, and capillary isoelectric focusing (cIEF).

In some embodiments, supernatants from expression systems which secrete recombinant protein into culture media can be first concentrated using a commercially available protein concentration filter, for example, an Amicon or Millipore Pellicon ultrafiltration unit. Following the concentration step, the concentrate can be applied to a suitable purification matrix. In some embodiments, an anion exchange resin can be employed, for example, a matrix or substrate having pendant diethylaminoethyl (DEAE) groups. The matrices can be acrylamide, agarose, dextran, cellulose, or other types commonly employed in protein purification. In some embodiments, a cation exchange step can be employed. Suitable cation exchangers include various insoluble matrices comprising sulfopropyl or carboxymethyl groups. In some embodiments, a hydroxyapatite media can be employed, including but not limited to, ceramic hydroxyapatite (CHT). In certain embodiments, one or more reverse-phase HPLC steps employing hydrophobic RP-HPLC media, e.g., silica gel having pendant methyl or other aliphatic groups, can be employed to further purify a recombinant protein (e.g., a MET-binding agent). Some or all of the foregoing purification steps, in various combinations, can be employed to provide a homogeneous recombinant protein.

In some embodiments, heterodimeric proteins such as bispecific agents described herein are purified according to

any of the methods described herein. In some embodiments, bispecific agents are isolated and/or purified using at least one chromatography step. In some embodiments, the at least one chromatography step comprises affinity chromatography. In some embodiments, the at least one chromatography step further comprises anion exchange chromatography. In some embodiments, the isolated and/or purified antibody product comprises at least 90% heterodimeric agent. In some embodiments, the isolated and/or purified product comprises at least 95%, 96%, 97%, 98% or 99% heterodimeric agent. In some embodiments, the isolated and/or purified product comprises about 100% heterodimeric agent.

In some embodiments, recombinant protein produced in bacterial culture can be isolated, for example, by initial extraction from cell pellets, followed by one or more concentration, salting-out, aqueous ion exchange, or size exclusion chromatography steps. HPLC can be employed for final purification steps. Microbial cells employed in expression of a recombinant protein can be disrupted by any convenient method, including freeze-thaw cycling, sonication, mechanical disruption, or use of cell lysing agents.

Methods known in the art for purifying antibodies and other proteins also include, for example, those described in U.S. Patent Publication Nos. 2008/0312425, 2008/0177048, and 2009/0187005.

In certain embodiments, a MET-binding agent is a polypeptide that is not an antibody. A variety of methods for identifying and producing non-antibody polypeptides that bind with high affinity to a protein target are known in the art. See, e.g., Skerra, 2007, *Curr. Opin. Biotechnol.*, 18:295-304; Hosse et al., 2006, *Protein Science*, 15:14-27; Gill et al., 2006, *Curr. Opin. Biotechnol.*, 17:653-658; Nygren, 2008, *FEBS J.*, 275:2668-76; and Skerra, 2008, *FEBS J.*, 275:2677-83. In certain embodiments, phage or mammalian cell display technology may be used to produce and/or identify a MET-binding polypeptide that is not an antibody. In certain embodiments, the polypeptide comprises a protein scaffold of a type selected from the group consisting of protein A, protein G, a lipocalin, a fibronectin domain, an ankyrin consensus repeat domain, and thioredoxin.

In certain embodiments, a MET-binding agent can be used in any one of a number of conjugated (i.e. an immunoconjugate or radioconjugate) or non-conjugated forms. In certain embodiments, the agent can be used in a non-conjugated form to harness the subject's natural defense mechanisms including complement-dependent cytotoxicity and antibody-dependent cellular toxicity to eliminate malignant or cancer cells.

In some embodiments, a MET-binding agent (e.g., an antibody or bispecific agent) is conjugated to a cytotoxic agent. In some embodiments, the cytotoxic agent is a chemotherapeutic agent including, but not limited to, methotrexate, adriamycin, doxorubicin, melphalan, mitomycin C, chlorambucil, daunorubicin or other intercalating agents. In some embodiments, the cytotoxic agent is an enzymatically active toxin of bacterial, fungal, plant, or animal origin, or fragments thereof, including, but not limited to, diphtheria A chain, non-binding active fragments of diphtheria toxin, exotoxin A chain, ricin A chain, abrin A chain, modeccin A chain, alpha-sarcin, Aleurites fordii proteins, dianthin proteins, Phytolacca americana proteins (PAPI, PAPII, and PAP-S), *Momordica charantia* inhibitor, curcumin, crotonin, *Saponaire officinalis* inhibitor, gelonin, mitogellin, restrictocin, phenomycin, enomycin, and the tricothecenes. In some embodiments, the cytotoxic agent is a radioisotope to produce a radioconjugate or a radioconjugated antibody. A variety of radionuclides are available for the production of radioconjugated antibodies

including, but not limited to, ^{90}Y , ^{125}I , ^{131}I , ^{123}I , ^{111}In , ^{131}In , ^{105}Rh , ^{153}Sm , ^{67}Cu , ^{67}Ga , ^{166}Ho , ^{177}Lu , ^{186}Re , ^{188}Re and ^{212}Bi . In some embodiments, conjugates of a binding agent described herein and one or more small molecule toxins, such as calicheamicins, maytansinoids, trichothecenes, and CC1065, and the derivatives of these toxins that have toxin activity, can also be used. In some embodiments, a binding agent described herein is conjugated to a maytansinoid. In some embodiments, a binding agent described herein is conjugated to mertansine (DM1). Conjugates of a binding agent described herein and a cytotoxic agent can be made using a variety of bifunctional protein-coupling agents including, but not limited to, N-succinimidyl-3-(2-pyridyldithiol) propionate (SPDP), iminothiolane (IT), bifunctional derivatives of imidoesters (such as dimethyl adipimidate HCl), active esters (such as disuccinimidyl suberate), aldehydes (such as glutaraldehyde), bis-azido compounds (such as bis(p-azidobenzoyl) hexanediamine), bis-diazonium derivatives (such as bis-(p-diazoniumbenzoyl)-ethylenediamine), diisocyanates (such as toluene 2,6-diisocyanate), and bis-active fluorine compounds (such as 1,5-difluoro-2,4-dinitrobenzene).

III. Polynucleotides

In certain embodiments, the invention encompasses polynucleotides comprising polynucleotides that encode a polypeptide (or a fragment of a polypeptide) that specifically binds MET, one or more components of the WNT pathway, or both MET and one or more components of the WNT pathway. The term "polynucleotides that encode a polypeptide" encompasses a polynucleotide which includes only coding sequences for the polypeptide, as well as a polynucleotide which includes additional coding and/or non-coding sequences. For example, in some embodiments, the invention provides a polynucleotide comprising a polynucleotide sequence that encodes an antibody to human MET or encodes a fragment of such an antibody (e.g., a fragment comprising the antigen-binding site). In some embodiments, the invention provides a polynucleotide comprising a polynucleotide sequence that encodes a polypeptide that binds one or more human FZD proteins or encodes a fragment of such a polypeptide (e.g., a fragment comprising the binding site). In some embodiments, the invention provides a polynucleotide comprising a polynucleotide sequence that encodes a polypeptide that binds one or more human WNT proteins or encodes a fragment of such a polypeptide (e.g., a fragment comprising the binding site). The polynucleotides of the invention can be in the form of RNA or in the form of DNA. DNA includes cDNA, genomic DNA, and synthetic DNA; and can be double-stranded or single-stranded, and if single-stranded can be the coding strand or non-coding (anti-sense) strand.

In certain embodiments, the polynucleotide comprises a polynucleotide encoding a polypeptide comprising a sequence selected from the group consisting of: SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:87, and SEQ ID NO:88. In some embodiments, the polynucleotide comprises a polynucleotide sequence selected from the group consisting of: SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:89, and SEQ ID NO:90. In some embodiments, the polynucleotide comprises the complement of a polynucleotide sequence selected from the group consisting of: SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO:20, SEQ ID NO:89, and SEQ ID NO:90.

In certain embodiments, the polynucleotide comprises a polynucleotide having a nucleotide sequence at least about 80% identical, at least about 85% identical, at least about 90%

identical, at least about 95% identical, and in some embodiments, at least about 96%, 97%, 98% or 99% identical to a polynucleotide comprising a sequence selected from the group consisting of: SEQ ID NO: 15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:89, and SEQ ID NO:90. Also provided is a polynucleotide that comprises a polynucleotide that hybridizes to SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:89, or SEQ ID NO:90. Also provided is a polynucleotide that comprises a polynucleotide that hybridizes to the complement of SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, and SEQ ID NO:20 or hybridizes to a complement of SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO: 17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:89, or SEQ ID NO:90. In certain embodiments, the hybridization is under conditions of high stringency.

The binding agents of the present invention can be encoded by one or more polynucleotides. For example, in some embodiments, a heavy chain polypeptide is encoded by one polynucleotide and a light chain polypeptide is encoded by a second polynucleotide. In some embodiments, a heavy chain polypeptide and a light chain polypeptide are encoded by one polynucleotide. In some embodiments, a heavy chain polypeptide is encoded by one polynucleotide, a light chain polypeptide is encoded by a second polynucleotide and a polypeptide comprising a soluble receptor is encoded by a third polynucleotide. In some embodiments, a heavy chain polypeptide and a light chain polypeptide are encoded by one polynucleotide and a polypeptide comprising a soluble receptor is encoded by a second polynucleotide. In some embodiments, three polypeptides are encoded from one polynucleotide. Thus, in some embodiments, a heavy chain polypeptide, a light chain polypeptide, and a polypeptide comprising a soluble receptor are encoded by a single polynucleotide.

In certain embodiments, the polynucleotides comprise the coding sequence for the mature polypeptide fused in the same reading frame to a polynucleotide which aids, for example, in expression and secretion of a polypeptide from a host cell (e.g., a leader sequence which functions as a secretory sequence for controlling transport of a polypeptide from the cell). The polypeptide having a leader sequence is a preproteins and can have the leader sequence cleaved by the host cell to form the mature form of the polypeptide. The polynucleotides can also encode for a proprotein which is the mature protein plus additional 5' amino acid residues. A mature protein having a prosequence is a proprotein and is an inactive form of the protein. Once the prosequence is cleaved an active mature protein remains.

In certain embodiments, the polynucleotides comprise the coding sequence for the mature polypeptide fused in the same reading frame to a marker sequence that allows, for example, for purification of the encoded polypeptide. For example, the marker sequence can be a hexa-histidine tag supplied by a pQE-9 vector to provide for purification of the mature polypeptide fused to the marker in the case of a bacterial host, or the marker sequence can be a hemagglutinin (HA) tag derived from the influenza hemagglutinin protein when a mammalian host (e.g., COS-7 cells) is used. In some embodiments, the marker sequence is a FLAG tag, a peptide of sequence DYKDDDDK (SEQ ID NO:73) which can be used in conjunction with other affinity tags.

The present invention further relates to variants of the hereinabove described polynucleotides encoding, for example, fragments, analogs, and/or derivatives.

In certain embodiments, the present invention provides polynucleotides comprising polynucleotides having a nucleotide sequence at least about 80% identical, at least about 85% identical, at least about 90% identical, at least about 95% identical, and in some embodiments, at least about 96%, 97%, 98% or 99% identical to a polynucleotide encoding a polypeptide comprising a MET-binding agent (e.g., an antibody or bispecific agent), or fragment thereof, described herein.

As used herein, the phrase a polynucleotide having a nucleotide sequence at least, for example, 95% "identical" to a reference nucleotide sequence is intended to mean that the nucleotide sequence of the polynucleotide is identical to the reference sequence except that the polynucleotide sequence can include up to five point mutations per each 100 nucleotides of the reference nucleotide sequence. In other words, to obtain a polynucleotide having a nucleotide sequence at least 95% identical to a reference nucleotide sequence, up to 5% of the nucleotides in the reference sequence can be deleted or substituted with another nucleotide, or a number of nucleotides up to 5% of the total nucleotides in the reference sequence can be inserted into the reference sequence. These mutations of the reference sequence can occur at the 5' or 3' terminal positions of the reference nucleotide sequence or anywhere between those terminal positions, interspersed either individually among nucleotides in the reference sequence or in one or more contiguous groups within the reference sequence.

The polynucleotide variants can contain alterations in the coding regions, non-coding regions, or both. In some embodiments, a polynucleotide variant contains alterations which produce silent substitutions, additions, or deletions, but does not alter the properties or activities of the encoded polypeptide. In some embodiments, a polynucleotide variant comprises silent substitutions that results in no change to the amino acid sequence of the polypeptide (due to the degeneracy of the genetic code). Polynucleotide variants can be produced for a variety of reasons, for example, to optimize codon expression for a particular host (i.e., change codons in the human mRNA to those preferred by a bacterial host such as *E. coli*). In some embodiments, a polynucleotide variant comprises at least one silent mutation in a non-coding or a coding region of the sequence.

In some embodiments, a polynucleotide variant is produced to modulate or alter expression (or expression levels) of the encoded polypeptide. In some embodiments, a polynucleotide variant is produced to increase expression of the encoded polypeptide. In some embodiments, a polynucleotide variant is produced to decrease expression of the encoded polypeptide. In some embodiments, a polynucleotide variant has increased expression of the encoded polypeptide as compared to a parental polynucleotide sequence. In some embodiments, a polynucleotide variant has decreased expression of the encoded polypeptide as compared to a parental polynucleotide sequence.

In some embodiments, at least one polynucleotide variant is produced (without changing the amino acid sequence of the encoded polypeptide) to increase production of a heterodimeric or heteromultimeric molecule. In some embodiments, at least one polynucleotide variant is produced (without changing the amino acid sequence of the encoded polypeptide) to increase production of a bispecific agent.

In certain embodiments, the polynucleotides are isolated. In certain embodiments, the polynucleotides are substantially pure.

Vectors and cells comprising the polynucleotides described herein are also provided. In some embodiments, an

expression vector comprises a polynucleotide. In some embodiments, a host cell comprises an expression vector comprising the polynucleotide. In some embodiments, a host cell comprises a polynucleotide.

IV. Methods Of Use And Pharmaceutical Compositions

The MET-binding agents (including antibodies and bispecific agents) of the invention that bind MET or MET and one or more components of the WNT pathway are useful in a variety of applications including, but not limited to, therapeutic treatment methods, such as the treatment of cancer. In certain embodiments, the agents are useful for inhibiting MET activity, inhibiting WNT pathway activity, inhibiting tumor growth, reducing tumor volume, reducing the frequency of cancer stem cells in a tumor, reducing the tumorigenicity of a tumor, inducing differentiation of tumor cells, inducing differentiation of cancer stem cells, inducing expression of differentiation markers on tumor cells, inducing expression of differentiation markers on cancer stem cells, inhibiting angiogenesis, and/or inhibiting EMT. The methods of use may be in vitro, ex vivo, or in vivo. In certain embodiments, a MET-binding agent is an antagonist of human MET. In certain embodiments, a MET-binding agent is an antagonist of one or more components of the WNT pathway. In certain embodiments, a MET-binding agent is an antagonist of both MET and one or more components of the WNT pathway.

The present invention provides methods for inhibiting growth of a tumor using the MET-binding agents described herein. In certain embodiments, the method of inhibiting growth of a tumor comprises contacting a tumor cell with a MET-binding agent (e.g., an antibody or a bispecific agent) in vitro. For example, an immortalized cell line or a cancer cell line is cultured in medium to which is added an antibody or a bispecific agent described herein to inhibit tumor cell growth. In some embodiments, tumor cells are isolated from a patient sample such as, for example, a tissue biopsy, pleural effusion, or blood sample and cultured in medium to which is added a binding agent to inhibit tumor cell growth.

In some embodiments, the method of inhibiting growth of a tumor comprises contacting a tumor or tumor cells with a MET-binding agent (e.g., an antibody or a bispecific agent) in vivo. In certain embodiments, contacting a tumor or tumor cell with a MET-binding agent is undertaken in an animal model. For example, an antibody or bispecific agent described herein may be administered to an immunocompromised host animal (e.g., NOD/SCID mice) that has a tumor xenograft. In some embodiments, tumor cells and/or cancer stem cells are isolated from a patient sample such as, for example, a tissue biopsy, pleural effusion, or blood sample and injected into an immunocompromised host animal (e.g., NOD/SCID mice) that is then administered a binding agent to inhibit tumor cell growth. In some embodiments, the MET-binding agent is administered at the same time or shortly after introduction of tumorigenic cells into the animal to prevent tumor growth ("preventative model"). In some embodiments, the MET-binding agent is administered as a therapeutic after tumors have grown to a specified size ("therapeutic model"). In certain embodiments, the MET-binding agent is a bispecific agent described herein that specifically binds human MET and one or more components of the WNT pathway. In certain embodiments, the MET-binding agent is a bispecific agent described herein that specifically binds human MET and one or more WNT proteins.

In certain embodiments, the method of inhibiting growth of a tumor in a subject comprises administering to the subject a therapeutically effective amount of a MET-binding agent described herein. In certain embodiments, the subject is a

human. In certain embodiments, the subject has a tumor or had a tumor that was removed. In certain embodiments, the tumor comprises cancer stem cells. In certain embodiments, the frequency of cancer stem cells in the tumor is reduced by administration of the MET-binding agent. The invention also provides a method of reducing the frequency of cancer stem cells in a tumor, comprising contacting the tumor with an effective amount of a MET-binding agent (e.g., an antibody or a bispecific agent) described herein. In some embodiments, a method of reducing the frequency of cancer stem cells in a tumor in a subject, comprises administering to the subject a therapeutically effective amount of a MET-binding agent described herein. In certain embodiments, the MET-binding agent is a bispecific agent described herein that specifically binds human MET and one or more components of the WNT pathway. In certain embodiments, the MET-binding agent is a bispecific agent described herein that specifically binds human MET and one or more WNT proteins.

The present invention further provides methods for inhibiting angiogenesis in a subject comprising administering a therapeutically effective amount of a MET-binding agent described herein to the subject. In some embodiments, the angiogenesis is tumor angiogenesis.

The present invention further provides methods for inhibiting epithelial-mesenchymal transition (EMT) of tumor cells comprising contacting tumor cells with an effective amount of a MET-binding agent described herein. The present invention further provides methods for inhibiting EMT of tumor cells in a subject comprising administering a therapeutically effective amount of a MET-binding agent described herein to the subject.

In some embodiments, the tumor is a solid tumor. In certain embodiments, the tumor is a tumor selected from the group consisting of colorectal tumor, colon tumor, pancreatic tumor, lung tumor, ovarian tumor, liver tumor, breast tumor, kidney tumor, prostate tumor, gastrointestinal tumor, melanoma, cervical tumor, bladder tumor, glioblastoma, and head and neck tumor. In certain embodiments, the tumor is a colorectal tumor or a colon tumor. In certain embodiments, the tumor is an ovarian tumor. In some embodiments, the tumor is a lung tumor. In certain embodiments, the tumor is a pancreatic tumor. In certain embodiments, the tumor is a breast tumor, including triple negative breast tumors. In some embodiments, the tumor is a glioblastoma.

The present invention further provides methods for treating cancer in a subject comprising administering a therapeutically effective amount of a MET-binding agent described herein to the subject. In some embodiments, the MET-binding agent binds MET, and inhibits or reduces cancer growth. In some embodiments, the MET-binding agent binds one or more components of the WNT pathway, and inhibits or reduces cancer growth. In some embodiments, the MET-binding agent is a bispecific agent that binds MET and one or more components of the WNT pathway, and inhibits or reduces cancer growth. In some embodiments, the MET-binding agent is a bispecific agent that binds MET and one or more components of the WNT pathway and provides dual inhibition of cancer involved signaling pathways. In some embodiments, the MET-binding agent binds MET, interferes with MET/HGF interactions, and inhibits or reduces cancer growth. In some embodiments, the MET-binding agent binds MET, blocks binding of MET to HGF, and inhibits or reduces cancer growth. In some embodiments, the MET-binding agent binds MET, inhibits angiogenesis, and inhibits or reduces cancer growth. In some embodiments, the MET-binding agent binds one or more components of the WNT pathway, interferes with WNT/FZD interactions, and inhibits

or reduces cancer growth. In some embodiments, the MET-binding agent binds both MET and one or more components of the WNT pathway, interferes with MET/HGF interactions and with WNT/FZD interactions, and inhibits or reduces cancer growth. In some embodiments, the MET-binding agent binds one or more WNT proteins and reduces the frequency of cancer stem cells in the cancer.

The present invention provides methods of treating cancer in a subject (e.g., a subject in need of treatment) comprising administering a therapeutically effective amount of a MET-binding agent described herein to the subject. In certain embodiments, the subject is a human. In certain embodiments, the subject has a cancerous tumor. In certain embodiments, the subject has had a tumor removed. The invention also provides a bispecific agent or antibody for use in a method of treating cancer, wherein the bispecific agent or antibody is an agent or antibody described herein. The invention also provides the use of a bispecific agent or antibody described herein for the manufacture of a medicament for the treatment of cancer.

In certain embodiments, the cancer is a cancer selected from the group consisting of colorectal cancer, pancreatic cancer, lung cancer, ovarian cancer, liver cancer, breast cancer, kidney cancer, prostate cancer, gastrointestinal cancer, melanoma, cervical cancer, bladder cancer, glioblastoma, and head and neck cancer. In certain embodiments, the cancer is ovarian cancer. In certain embodiments, the cancer is colorectal cancer or colon cancer. In certain embodiments, the cancer is pancreatic cancer. In certain embodiments, the cancer is breast cancer, including triple negative breast cancer. In certain embodiments, the cancer is prostate cancer. In certain embodiments, the cancer is lung cancer, including non-small cell lung cancer and small cell lung cancer.

In some embodiments, the subject's cancer/tumor may be refractory to certain treatment(s). As a non-limiting example, the subject's cancer (or tumor) may be chemorefractory. In some embodiments, the subject's cancer may be resistant to EGFR inhibitors.

Methods of treating a disease or disorder in a subject, wherein the disease or disorder is characterized by an increased level of stem cells and/or progenitor cells are further provided. In some embodiments, the treatment methods comprise administering a therapeutically effective amount of a MET-binding agent, polypeptide, or antibody described herein to the subject.

In certain embodiments of any of the methods described herein, the MET-binding agent is a bispecific agent that specifically binds human MET and one or more components of the WNT pathway. In some embodiments, the bispecific agent comprises a first binding site that specifically binds human MET and a second binding site that specifically binds one or more components of the human WNT pathway, wherein the first binding site comprises a heavy chain CDR1 comprising ASYAWS (SEQ ID NO:1), a heavy chain CDR2 comprising YISYSGGTDYNPSLKS (SEQ ID NO:2), and a heavy chain CDR3 comprising KGAY (SEQ ID NO:3), and a light chain CDR1 comprising SASSSVSSSYLY (SEQ ID NO:4), a light chain CDR2 comprising STSNLAS (SEQ ID NO:5), and a light chain CDR3 comprising HQWSSYPYT (SEQ ID NO:6). In some embodiments, the bispecific agent comprises a first binding site that specifically binds human MET and a second binding site that specifically binds one or more components of the human WNT pathway, wherein the first antigen-binding site comprises a heavy chain CDR1 comprising GYTFTSYWLH (SEQ ID NO:78), a heavy chain CDR2 comprising GMIDPSNSDTRFNPNFKD (SEQ ID NO:79), and a heavy chain CDR3 comprising TYGSYVS-

PLDY (SEQ ID NO:81), SYGSYVSPLDY (SEQ ID NO:82), ATYGSYVSPLDY (SEQ ID NO:83), or XYGSYVSPLDY (SEQ ID NO:80), wherein X is not R; and a light chain CDR1 comprising KSSQSLYTSSQKNYLA (SEQ ID NO:84), a light chain CDR2 comprising WASTRES (SEQ ID NO:85), and a light chain CDR3 comprising QQYYAYPWT (SEQ ID NO:86).

In certain embodiments of any of the methods described herein, the MET-binding agent is a bispecific agent that comprises a heavy chain variable region having at least about 80% sequence identity to SEQ ID NO:7 and a light chain variable region having at least about 80% sequence identity to SEQ ID NO:8.

In some embodiments of any of the methods described herein, the MET-binding agent is an antibody. In some embodiments, the anti-MET antibody comprises the heavy chain variable region and the light chain variable region of antibody 73R009. In some embodiments, the anti-MET antibody is antibody 73R009. In some embodiments, the anti-MET antibody is a monovalent version of antibody 73R009. In some embodiments, the anti-MET antibody is an antibody comprising a heavy chain variable region encoded by the plasmid deposited with ATCC as PTA-13609 and a light chain variable region encoded by the plasmid deposited with ATCC as PTA-13610. In some embodiments, the MET-binding agent is a bispecific agent comprising an antigen-binding site from antibody 73R009. In some embodiments, the MET-binding agent is a bispecific agent comprising a heavy chain variable region encoded by the plasmid deposited with ATCC as PTA-13609 and a light chain variable region encoded by the plasmid deposited with ATCC as PTA-13610. In some embodiments, the MET-binding agent is a bispecific agent comprising a first arm comprising the heavy chain variable region and the light chain variable region of antibody 73R009 and a second arm comprising a FZD8 Fri domain. In some embodiments, the MET-binding agent is a bispecific agent comprising a first arm comprising the heavy chain variable region and the light chain variable region of antibody 73R009 and a second arm comprising a FZD8 Fri domain and a human Fc region. In some embodiments, the MET-binding agent is bispecific agent 315B6. In some embodiments, the MET-binding agent is a bispecific agent comprising SEQ ID NO:7, SEQ ID NO:8, and SEQ ID NO:28. In some embodiments, the MET-binding agent is a bispecific agent comprising SEQ ID NO:7, SEQ ID NO:8, and SEQ ID NO:29. In some embodiments, the MET-binding agent is a bispecific agent comprising SEQ ID NO:7, SEQ ID NO:8, and SEQ ID NO:39. In some embodiments, the MET-binding agent is a bispecific agent comprising SEQ ID NO:13, SEQ ID NO:14, and SEQ ID NO:56. In some embodiments, the MET-binding agent is a bispecific agent, wherein a first arm of the bispecific agent comprises SEQ ID NO:13 and SEQ ID NO:14; and a second arm of the bispecific agent comprises SEQ ID NO:56.

In certain embodiments, the methods further comprise a step of determining the level of MET expression in the tumor or cancer. In some embodiments, the level of expression of MET in a tumor or cancer is compared to the level of expression of MET in a reference sample. As used herein, a "reference sample" includes but is not limited to, normal tissue, non-cancerous tissue of the same tissue type, tumor tissue of the same tissue type, and tumor tissue of a different tissue type. Thus, in some embodiments, the level of expression of MET in a tumor or cancer is compared to the level of expression of MET in normal tissue. In some embodiments, the level of expression of MET in a tumor or cancer is compared to the level of expression of MET in non-cancerous tissue of the same tissue type. In some embodiments, the level of expres-

sion of MET in a tumor or cancer is compared to the level of expression of MET in tumors or cancers of the same tissue type. In some embodiments, the level of expression of MET in a tumor or cancer is compared to the level of expression of MET in tumors or cancers of a different tissue type. In some embodiments, the level of expression of MET in a tumor or cancer is compared to a pre-determined level of MET. In some embodiments, determining the level of MET expression is done prior to treatment. In some embodiments, determining the level of MET expression is by immunohistochemistry. In some embodiments, the subject is administered a MET-binding agent described herein if the tumor or cancer has an elevated level of MET expression as compared to the expression of MET in normal tissue or non-cancerous tissue of the same tissue type. For example, in some embodiments, the subject is administered a MET-binding agent (e.g., bispecific agent 315B6) if the tumor or cancer has an elevated level of MET expression as compared to the level of MET expression in a reference sample. In some embodiments, the subject is administered a MET-binding agent described herein if the tumor or cancer has an elevated level of MET expression as compared to the pre-determined level of MET.

In addition, the present invention provides methods of identifying a human subject for treatment with a MET-binding agent, comprising determining if the subject has a tumor that has an elevated level of MET expression as compared to expression of MET in a reference sample. In some embodiments, the reference sample is normal tissue or non-cancerous tissue of the same tissue type. In some embodiments, the reference sample is tumor/cancer tissue of the same tissue type. In some embodiments, the reference sample is tumor/cancer tissue of a different tissue type. In some embodiments, the level of expression of MET in a tumor or cancer is compared to a pre-determined level of MET. In some embodiments, if the tumor has an elevated level of MET expression the subject is selected for treatment with an agent that specifically binds MET. In some embodiments, if selected for treatment, the subject is administered a MET-binding agent described herein. In certain embodiments, the subject has had a tumor removed. For example, in some embodiments, the expression level of MET in a tumor is determined, if the tumor has an elevated level of MET expression as compared to the level of MET in a reference sample or a pre-determined level, the subject is selected for treatment with an agent that specifically binds MET. If selected for treatment, the subject is administered a MET-binding agent described herein. In some embodiments, the MET-binding agent is antibody 73R009 or a monovalent version thereof. In some embodiments, the MET-binding agent is an anti-MET/FZD-Fc bispecific agent. In some embodiments, the MET-binding agent is an anti-MET/FZD8-Fc bispecific agent. In some embodiments, the MET-binding agent is bispecific agent 315B6.

The present invention provides methods of selecting a human subject for treatment with a MET-binding agent, comprising determining if the subject has a tumor that has an elevated expression level of MET. In some embodiments, the methods of selecting a human subject for treatment with a MET-binding agent comprise determining if the subject has a tumor that has an elevated expression level of MET, wherein if the tumor has an elevated expression level of MET, the subject is selected for treatment with an agent that specifically binds MET. The present invention provides methods of selecting a human subject for treatment with a MET-binding agent, comprising determining if the subject has a tumor that has a high expression level of MET. In some embodiments, the methods of selecting a human subject for treatment with a MET-binding agent comprise determining if the subject has a

tumor that has a high expression level of MET, wherein if the tumor has a high expression level of MET the subject is selected for treatment with an agent that specifically binds MET. In some embodiments, the “elevated” or “high” expression level is in comparison to the expression level of MET in normal tissue of the same tissue type. In some embodiments, the “elevated” or “high” expression level is in comparison to the expression level of MET in other tumors of the same tissue type. In some embodiments, the “elevated” or “high” expression level is in comparison to the expression level of MET in a reference sample. In some embodiments, the “elevated” or “high” expression level is in comparison to a pre-determined level of MET. In some embodiments, if selected for treatment, the subject is administered a MET-binding agent described herein. In certain embodiments, the subject has had a tumor removed. In some embodiments, the MET-binding agent is an anti-MET antibody. In some embodiments, the anti-MET antibody is antibody 73R009 or a monovalent version thereof. In some embodiments, the MET-binding agent is an anti-MET/FZD-Fc bispecific agent. In some embodiments, the MET-binding agent is an anti-MET/FZD8-Fc bispecific agent. In some embodiments, the anti-MET/FZD-Fc bispecific agent is 315B6.

The present invention also provides methods of treating cancer in a human subject, comprising: (a) selecting a subject for treatment based, at least in part, on the subject having a cancer that has an elevated or high expression level of MET, and (b) administering to the subject a therapeutically effective amount of a MET-binding agent described herein.

Methods for determining the level of MET expression in a cell, tumor, or cancer are known by those of skill in the art. For nucleic acid expression these methods include, but are not limited to, PCR-based assays, microarray analyses, and nucleotide sequencing (e.g., NextGen sequencing). For protein expression, these methods include, but are not limited to, Western blot analysis, protein arrays, ELISAs, immunohistochemistry (IHC) assays, and FACS analysis.

Methods for determining whether a tumor or cancer has an elevated or high level of MET expression can use a variety of samples. In some embodiments, the sample is taken from a subject having a tumor or cancer. In some embodiments, the sample is a fresh tumor/cancer sample. In some embodiments, the sample is a frozen tumor/cancer sample. In some embodiments, the sample is a formalin-fixed paraffin-embedded sample. In some embodiments, the sample is processed to a cell lysate. In some embodiments, the sample is processed to DNA or RNA.

The present invention further provides pharmaceutical compositions comprising the binding agents described herein. In certain embodiments, the pharmaceutical compositions further comprise a pharmaceutically acceptable vehicle. These pharmaceutical compositions find use in inhibiting tumor growth and/or treating cancer in a subject (e.g., a human patient).

In certain embodiments, the invention provides pharmaceutical compositions comprising bispecific agents, wherein at least about 90%, at least about 95%, at least about 98%, at least about 99% of the agents in the composition are bispecific agents or heterodimeric agents. In certain embodiments, the bispecific agents are IgG (e.g., IgG2 or IgG1) based agents. In certain embodiments, the bispecific agents are IgG2-based agents. In certain embodiments, less than about 10%, less than about 5%, less than about 2%, or less than about 1% of the total agents in the composition are monospecific agents or homodimeric agents. In certain embodiments, the agents in the composition are at least about 98% heterodimeric.

In certain embodiments, formulations are prepared for storage and use by combining a purified antibody or agent of the present invention with a pharmaceutically acceptable vehicle (e.g., a carrier or excipient). Suitable pharmaceutically acceptable vehicles include, but are not limited to, non-toxic buffers such as phosphate, citrate, and other organic acids; salts such as sodium chloride; antioxidants including ascorbic acid and methionine; preservatives such as octadecyltrimethylbenzyl ammonium chloride, hexamethonium chloride, benzalkonium chloride, benzethonium chloride, phenol, butyl or benzyl alcohol, alkyl parabens, such as methyl or propyl paraben, catechol, resorcinol, cyclohexanol, 3-pentanol, and m-cresol; low molecular weight polypeptides (e.g., less than about 10 amino acid residues); proteins such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, histidine, arginine, or lysine; carbohydrates such as monosaccharides, disaccharides, glucose, mannose, or dextrans; chelating agents such as EDTA; sugars such as sucrose, mannitol, trehalose or sorbitol; salt-forming counter-ions such as sodium; metal complexes such as Zn-protein complexes; and non-ionic surfactants such as TWEEN or polyethylene glycol (PEG). (*Remington: The Science and Practice of Pharmacy*, 22nd Edition, 2012, Pharmaceutical Press, London).

The pharmaceutical compositions of the present invention can be administered in any number of ways for either local or systemic treatment. Administration can be topical by epidermal or transdermal patches, ointments, lotions, creams, gels, drops, suppositories, sprays, liquids, and powders; pulmonary by inhalation or insufflation of powders or aerosols, including by nebulizer, intratracheal, and intranasal; oral; or parenteral including intravenous, intraarterial, intratumoral, subcutaneous, intraperitoneal, intramuscular (e.g., injection or infusion), or intracranial (e.g., intrathecal or intraventricular).

The therapeutic formulation can be in unit dosage form. Such formulations include tablets, pills, capsules, powders, granules, solutions or suspensions in water or non-aqueous media, or suppositories. In solid compositions such as tablets the principal active ingredient is mixed with a pharmaceutical carrier. Conventional tableting ingredients include corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and diluents (e.g., water). These can be used to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a non-toxic pharmaceutically acceptable salt thereof. The solid preformulation composition is then subdivided into unit dosage forms of a type described above. The tablets, pills, etc. of the formulation or composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner composition covered by an outer component. Furthermore, the two components can be separated by an enteric layer that serves to resist disintegration and permits the inner component to pass intact through the stomach or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials include a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The MET-binding agents described herein can also be entrapped in microcapsules. Such microcapsules are prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatin-microcapsules and poly-(methylmethacrylate) microcapsules, respectively, in colloidal drug delivery systems (for

example, liposomes, albumin microspheres, microemulsions, nanoparticles and nanocapsules) or in macroemulsions as described in *Remington: The Science and Practice of Pharmacy*, 22nd Edition, 2012, Pharmaceutical Press, London.

In certain embodiments, pharmaceutical formulations include a MET-binding agent (e.g., an antibody or a bispecific agent) of the present invention complexed with liposomes. Methods to produce liposomes are known to those of skill in the art. For example, some liposomes can be generated by reverse phase evaporation with a lipid composition comprising phosphatidylcholine, cholesterol, and PEG-derivatized phosphatidylethanolamine (PEG-PE). Liposomes can be extruded through filters of defined pore size to yield liposomes with the desired diameter.

In certain embodiments, sustained-release preparations can be produced. Suitable examples of sustained-release preparations include semi-permeable matrices of solid hydrophobic polymers containing a MET-binding agent (e.g., an antibody or a bispecific agent), where the matrices are in the form of shaped articles (e.g., films or microcapsules). Additional examples of sustained-release matrices include polyesters, hydrogels such as poly(2-hydroxyethyl-methacrylate) or poly(vinyl alcohol), polylactides, copolymers of L-glutamic acid and 7 ethyl-L-glutamate, non-degradable ethylene-vinyl acetate, degradable lactic acid-glycolic acid copolymers such as the LUPRON DEPOTTM (injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate), sucrose acetate isobutyrate, and poly-D-(-)-3-hydroxybutyric acid.

In certain embodiments, in addition to administering a MET-binding agent described herein (e.g., an antibody or bispecific agent), a method or treatment further comprises administering at least one additional therapeutic agent. An additional therapeutic agent can be administered prior to, concurrently with, and/or subsequently to, administration of the MET-binding agent. Pharmaceutical compositions comprising a MET-binding agent and the additional therapeutic agent(s) are also provided. In some embodiments, the at least one additional therapeutic agent comprises 1, 2, 3, or more additional therapeutic agents.

Combination therapy with at least two therapeutic agents often uses agents that work by different mechanisms of action, although this is not required. Combination therapy using agents with different mechanisms of action may result in additive or synergetic effects. Combination therapy may allow for a lower dose of each agent than is used in monotherapy, thereby reducing toxic side effects and/or increasing the therapeutic index of at least one of the agents. Combination therapy may decrease the likelihood that resistant cancer cells will develop. In some embodiments, combination therapy comprises a therapeutic agent that primarily affects (e.g., inhibits or kills) non-tumorigenic cells and a therapeutic agent that primarily affects (e.g., inhibits or kills) tumorigenic CSCs.

Useful classes of therapeutic agents include, for example, anti-tubulin agents, auristatins, DNA minor groove binders, DNA replication inhibitors, alkylating agents (e.g., platinum complexes such as cisplatin, mono(platinum), bis(platinum) and tri-nuclear platinum complexes and carboplatin), anthracyclines, antibiotics, antifolates, antimetabolites, chemotherapy sensitizers, duocarmycins, etoposides, fluorinated pyrimidines, ionophores, lexitropsins, nitrosoureas, platinum, purine antimetabolites, puromycins, radiation sensitizers, steroids, taxanes, topoisomerase inhibitors, vinca alkaloids, or the like. In certain embodiments, the second therapeutic agent is an alkylating agent, an anti-metabolite, an anti-mitotic, a topoisomerase inhibitor, or an angiogenesis

inhibitor. In some embodiments, the second therapeutic agent is a platinum complex such as carboplatin or cisplatin. In some embodiments, the additional therapeutic agent is a platinum complex in combination with a taxane.

Therapeutic agents that may be administered in combination with the MET-binding agents include chemotherapeutic agents. Thus, in some embodiments, the method or treatment involves the administration of a MET-binding agent of the present invention in combination with a chemotherapeutic agent or cocktail of multiple different chemotherapeutic agents. In some embodiments, the method or treatment involves the administration of a bispecific agent of the present invention that binds MET and one or more WNT proteins in combination with a chemotherapeutic agent or cocktail of multiple different chemotherapeutic agents.

Chemotherapeutic agents useful in the instant invention include, but are not limited to, alkylating agents such as thiopeta and cyclophosphamide (CYTOXAN); alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, trietylenephosphoramide, triethylenethiophosphoramide and trimethylolomelamine; nitrogen mustards such as chlorambucil, chlornaphazine, chlorthophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melfhalan, novembichin, phenesterine, prednimustine, trofosfamide, doxorubicin, epirubicin, esorubicin, idarubicin, marcellomyacin, mitomycins, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate and 5-fluorouracil (5-FU); folic acid analogues such as deneropterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytosine arabinoside, dideoxyuridine, doxifluridine, enocitabine, floxuridine, 5-FU; androgens such as calusterone, dromostanolone propionate, epitostanol, mepitiostane, testolactone; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenishers such as folinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; amsacrine; bestabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elformithine; elliptinium acetate; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidamine; mitoguazone; mitoxantrone; mopidamol; nitracrine; pentostatin; phenamet; pirarubicin; podophyllinic acid; 2-ethylhydrazide; procarbazine; PSK; razoxane; sizofuran; spirogermanium; tenuazonic acid; triaziquone; 2,2',2"-trichlorotriethylamine; urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside (Ara-C); taxoids, e.g. paclitaxel (TAXOL) and docetaxel (TAXOTERE); chlorambucil; gemcitabine; 6-thioguanine; mercaptopurine; platinum analogs such as cisplatin and carboplatin; vinblastine; platinum; etoposide (VP-16); ifosfamide; mitomycin C; mitoxantrone; vincristine; vinorelbine; navelbine; novantrone; teniposide; daunomycin; aminopterin; ibandronate; CPT11; topoisomerase inhibitor RFS 2000; difluoromethylornithine (DMFO); retinoic acid; esperamicins; capecitabine (XELODA); and pharmaceutically acceptable salts, acids or

derivatives of any of the above. Chemotherapeutic agents also include anti-hormonal agents that act to regulate or inhibit hormone action on tumors such as anti-estrogens including, for example, tamoxifen, raloxifene, aromatase inhibiting 4(5)-imidazoles, 4-hydroxytamoxifen, trioxifene, keoxifene, LY117018, onapristone, and toremifene (FARESTON); and anti-androgens such as flutamide, nilutamide, bicalutamide, leuprolide, and goserelin; and pharmaceutically acceptable salts, acids or derivatives of any of the above. In certain embodiments, the second therapeutic agent is cisplatin. In certain embodiments, the second therapeutic agent is carboplatin. In certain embodiments, the second therapeutic agent is paclitaxel.

In certain embodiments, the chemotherapeutic agent is a topoisomerase inhibitor. Topoisomerase inhibitors are chemotherapeutic agents that interfere with the action of a topoisomerase enzyme (e.g., topoisomerase I or II). Topoisomerase inhibitors include, but are not limited to, doxorubicin HCl, daunorubicin citrate, mitoxantrone HCl, actinomycin D, etoposide, topotecan HCl, teniposide (VM-26), and irinotecan, as well as pharmaceutically acceptable salts, acids, or derivatives of any of these. In certain embodiments, the second therapeutic agent is irinotecan.

In certain embodiments, the chemotherapeutic agent is an anti-metabolite. An anti-metabolite is a chemical with a structure that is similar to a metabolite required for normal biochemical reactions, yet different enough to interfere with one or more normal functions of cells, such as cell division. Anti-metabolites include, but are not limited to, gemcitabine, fluorouracil, capecitabine, methotrexate sodium, raltitrexed, pemetrexed, tegafur, cytosine arabinoside, thioguanine, 5-azacytidine, 6-mercaptopurine, azathioprine, 6-thioguanine, pentostatin, fludarabine phosphate, and cladribine, as well as pharmaceutically acceptable salts, acids, or derivatives of any of these. In certain embodiments, the second therapeutic agent is gemcitabine.

In certain embodiments, the chemotherapeutic agent is an anti-mitotic agent, including, but not limited to, agents that bind tubulin. In some embodiments, the agent is a taxane. In certain embodiments, the agent is paclitaxel or docetaxel, or a pharmaceutically acceptable salt, acid, or derivative of paclitaxel or docetaxel. In certain embodiments, the agent is paclitaxel (TAXOL), docetaxel (TAXOTERE), albumin-bound paclitaxel (ABRAXANE), DHA-paclitaxel, or PG-paclitaxel. In certain alternative embodiments, the anti-mitotic agent comprises a vinca alkaloid, such as vincristine, binblastine, vinorelbine, or vindesine, or pharmaceutically acceptable salts, acids, or derivatives thereof. In some embodiments, the anti-mitotic agent is an inhibitor of kinesin Eg5 or an inhibitor of a mitotic kinase such as Aurora A or Plk1. In certain embodiments, where the chemotherapeutic agent administered in combination with a MET-binding agent is an anti-mitotic agent, the cancer or tumor being treated is breast cancer or a breast tumor.

In some embodiments, an additional therapeutic agent comprises an agent such as a small molecule. For example, treatment can involve the combined administration of a MET-binding agent (e.g. an antibody or bispecific agent) of the present invention with a small molecule that acts as an inhibitor against additional tumor-associated proteins including, but not limited to, EGFR, ErbB2, HER2, and/or MET. In certain embodiments, the additional therapeutic agent is a small molecule that inhibits a cancer stem cell pathway. In some embodiments, the additional therapeutic agent is a small molecule inhibitor of the NOTCH pathway. In some embodiments, the additional therapeutic agent is a small molecule inhibitor of the WNT pathway. In some embodiments,

the additional therapeutic agent is a small molecule inhibitor of the BMP pathway. In some embodiments, the additional therapeutic agent is a small molecule that inhibits β -catenin signaling.

In some embodiments, an additional therapeutic agent comprises a biological molecule, such as an antibody. For example, treatment can involve the combined administration of a MET-binding agent (e.g. an antibody or bispecific agent) of the present invention with other antibodies against additional tumor-associated proteins including, but not limited to, antibodies that bind EGFR, ErbB2, and/or HER2. In certain embodiments, the additional therapeutic agent is an antibody that is an anti-cancer stem cell marker antibody. In some embodiments, the additional therapeutic agent is an antibody that binds a component of the NOTCH pathway. In some embodiments, the additional therapeutic agent is an antibody that binds a component of the WNT pathway. In certain embodiments, the additional therapeutic agent is an antibody that inhibits a cancer stem cell pathway. In some embodiments, the additional therapeutic agent is an antibody inhibitor of the NOTCH pathway. In some embodiments, the additional therapeutic agent is an antibody inhibitor of the WNT pathway. In some embodiments, the additional therapeutic agent is an antibody inhibitor of the BMP pathway. In some embodiments, the additional therapeutic agent is an antibody that inhibits β -catenin signaling. In certain embodiments, the additional therapeutic agent is an antibody that is an angiogenesis inhibitor or modulator (e.g., an anti-VEGF or VEGF receptor antibody). In certain embodiments, the additional therapeutic agent is bevacizumab (AVASTIN), trastuzumab (HERCEPTIN), panitumumab (VECTIBIX), or cetuximab (ERBITUX). Combined administration can include co-administration, either in a single pharmaceutical formulation or using separate formulations, or consecutive administration in either order but generally within a time period such that all active agents can exert their biological activities simultaneously.

Furthermore, treatment with a MET-binding agent described herein can include combination treatment with other biologic molecules, such as one or more cytokines (e.g., lymphokines, interleukins, tumor necrosis factors, and/or growth factors) or can be accompanied by surgical removal of tumors, cancer cells, or any other therapy deemed necessary by a treating physician.

In certain embodiments, the treatment involves the administration of a MET-binding agent (e.g. an antibody or bispecific agent) of the present invention in combination with radiation therapy. Treatment with a MET-binding agent can occur prior to, concurrently with, or subsequent to administration of radiation therapy. Dosing schedules for such radiation therapy can be determined by the skilled medical practitioner.

It will be appreciated that the combination of a MET-binding agent and an additional therapeutic agent may be administered in any order or concurrently. Treatment with a MET-binding agent (e.g., an antibody or a bispecific agent) can occur prior to, concurrently with, or subsequent to administration of chemotherapies. Combined administration can include co-administration, either in a single pharmaceutical formulation or using separate formulations, or consecutive administration in either order but generally within a time period such that all active agents can exert their biological activities simultaneously. Preparation and dosing schedules for such chemotherapeutic agents can be used according to manufacturers' instructions or as determined empirically by the skilled practitioner. Preparation and dosing schedules for such chemotherapy are also described in *The Chemotherapy*

Source Book, 4th Edition, 2008, M. C. Perry, Editor, Lippincott, Williams & Wilkins, Philadelphia, Pa.

In some embodiments, the MET-binding agent will be administered to patients that have previously undergone treatment with therapeutic agents. In certain other embodiments, the MET-binding agent and an additional therapeutic agent will be administered substantially simultaneously or concurrently. For example, a subject may be given a MET-binding agent (e.g., an antibody or bispecific agent) while undergoing a course of treatment with a second therapeutic agent (e.g., chemotherapy). In certain embodiments, a MET-binding agent will be administered within 1 year of the treatment with a second therapeutic agent. In certain alternative embodiments, a MET-binding agent will be administered within 10, 8, 6, 4, or 2 months of any treatment with a second therapeutic agent. In certain other embodiments, a MET-binding agent will be administered within 4, 3, 2, or 1 weeks of any treatment with a second therapeutic agent. In some embodiments, a MET-binding agent will be administered within 5, 4, 3, 2, or 1 days of any treatment with a second therapeutic agent. It will further be appreciated that the two (or more) agents or treatments may be administered to the subject within a matter of hours or minutes (i.e., substantially simultaneously).

For the treatment of a disease, the appropriate dosage of a MET-binding agent (e.g., an antibody or bispecific agent) of the present invention depends on the type of disease to be treated, the severity and course of the disease, the responsiveness of the disease, whether the MET-binding agent is administered for therapeutic or preventative purposes, previous therapy, the patient's clinical history, and so on, all at the discretion of the treating physician. The MET-binding agent can be administered one time or as a series of treatments spread over several days to several months, or until a cure is effected or a diminution of the disease state is achieved (e.g., reduction in tumor size). Optimal dosing schedules can be calculated from measurements of drug accumulation in the body of the patient and will vary depending on the relative potency of an individual antibody or agent. The administering physician can determine optimum dosages, dosing methodologies, and repetition rates. In certain embodiments, dosage of a MET-binding agent is from about 0.01 µg to about 100 mg/kg of body weight, from about 0.1 µg to about 100 mg/kg of body weight, from about 1 µg to about 100 mg/kg of body weight, from about 1 mg to about 100 mg/kg of body weight, about 1 mg to about 80 mg/kg of body weight from about 10 mg to about 100 mg/kg of body weight, from about 10 mg to about 75 mg/kg of body weight, or from about 10 mg to about 50 mg/kg of body weight. In certain embodiments, the dosage of the MET-binding agent is from about 0.1 mg to about 20 mg/kg of body weight. In certain embodiments, dosage can be given once or more daily, weekly, monthly, or yearly. In certain embodiments, the MET-binding agent is given once every week, once every two weeks, once every three weeks, or once every month.

In some embodiments, a MET-binding agent (e.g., an antibody or bispecific agent) may be administered at an initial higher "loading" dose, followed by one or more lower doses. In some embodiments, the frequency of administration may also change. In some embodiments, a dosing regimen may comprise administering an initial dose, followed by additional doses (or "maintenance" doses) once a week, once every two weeks, once every three weeks, or once every month. For example, a dosing regimen may comprise administering an initial loading dose, followed by a weekly maintenance dose of, for example, one-half of the initial dose. Or a dosing regimen may comprise administering an initial loading dose, followed by maintenance doses of, for example

one-half of the initial dose every other week. Or a dosing regimen may comprise administering three initial doses for 3 weeks, followed by maintenance doses of, for example, the same amount every other week. Or a dosing regimen may comprise administering an initial dose followed by additional doses every 3 weeks or once a month. The treating physician can estimate repetition rates for dosing based on measured residence times and concentrations of the drug in bodily fluids or tissues. The progress of therapy can be monitored by conventional techniques and assays.

As is known to those of skill in the art, administration of any therapeutic agent may lead to side effects and/or toxicities. In some cases, the side effects and/or toxicities are so severe as to preclude administration of the particular agent at a therapeutically effective dose. In some cases, drug therapy must be discontinued, and other agents may be tried. However, many agents in the same therapeutic class often display similar side effects and/or toxicities, meaning that the patient either has to stop therapy, or if possible, suffer from the unpleasant side effects associated with the therapeutic agent.

Side effects from therapeutic agents may include, but are not limited to, hives, skin rashes, itching, nausea, vomiting, decreased appetite, diarrhea, chills, fever, fatigue, muscle aches and pain, headaches, low blood pressure, high blood pressure, hypokalemia, bone effects, low blood counts, bleeding, and cardiovascular problems.

Thus, one aspect of the present invention is directed to methods of treating cancer in a patient comprising administering a MET-binding agent described herein using an intermittent dosing regimen, which may reduce side effects and/or toxicities associated with administration of the agent. As used herein, "intermittent dosing" refers to a dosing regimen using a dosing interval of more than once a week, e.g., dosing once every 2 weeks, once every 3 weeks, once every 4 weeks, etc. In some embodiments, a method for treating cancer in a human patient comprises administering to the patient an effective dose of a MET-binding agent (e.g., an antibody or a bispecific agent) described herein according to an intermittent dosing regimen. In some embodiments, a method for treating cancer in a human patient comprises administering to the patient an effective dose of a MET-binding agent (e.g., an antibody or a bispecific agent) according to an intermittent dosing regimen, and increasing the therapeutic index of the MET-binding agent. In some embodiments, the intermittent dosing regimen comprises administering an initial dose of a MET-binding agent (e.g., an antibody or a bispecific agent) to the patient, and administering subsequent doses of the MET-binding agent about once every 2 weeks. In some embodiments, the intermittent dosing regimen comprises administering an initial dose of a MET-binding agent (e.g., an antibody or a bispecific agent) to the patient, and administering subsequent doses of the MET-binding agent about once every 3 weeks. In some embodiments, the intermittent dosing regimen comprises administering an initial dose of a MET-binding agent (e.g., an antibody or a bispecific agent) to the patient, and administering subsequent doses of the MET-binding agent about once every 4 weeks.

In some embodiments, the subsequent doses in an intermittent dosing regimen are about the same amount or less than the initial dose. In other embodiments, the subsequent doses are a greater amount than the initial dose. As is known by those of skill in the art, doses used will vary depending on the clinical goals to be achieved. In some embodiments, the initial dose is about 0.25 mg/kg to about 20 mg/kg. In some embodiments, the initial dose is about 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 mg/kg. In certain embodiments, the initial dose is about 0.5 mg/kg. In certain

embodiments, the initial dose is about 1 mg/kg. In certain embodiments, the initial dose is about 2.5 mg/kg. In certain embodiments, the initial dose is about 5 mg/kg. In certain embodiments, the initial dose is about 7.5 mg/kg. In certain embodiments, the initial dose is about 10 mg/kg. In certain embodiments, the initial dose is about 12.5 mg/kg. In certain embodiments, the initial dose is about 15 mg/kg. In certain embodiments, the initial dose is about 20 mg/kg. In some embodiments, the subsequent doses are about 0.25 mg/kg to about 15 mg/kg. In certain embodiments, the subsequent doses are about 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15 mg/kg. In certain embodiments, the subsequent doses are about 0.5 mg/kg. In certain embodiments, the subsequent doses are about 1 mg/kg. In certain embodiments, the subsequent doses are about 2.5 mg/kg. In certain embodiments, the subsequent doses are about 5 mg/kg. In some embodiments, the subsequent doses are about 7.5 mg/kg. In some embodiments, the subsequent doses are about 10 mg/kg. In some embodiments, the subsequent doses are about 12.5 mg/kg.

Thus the present invention provides methods for reducing toxicity of a MET-binding agent (e.g., an antibody or a bispecific agent) described herein in a human patient that comprise administering to the patient the MET-binding agent using an intermittent dosing regimen. Also provided are methods for reducing side effects of a MET-binding agent (e.g., an antibody or a bispecific agent) in a human patient that comprise administering to the patient the MET-binding agent using an intermittent dosing regimen. Also provided are methods for increasing the therapeutic index of a MET-binding agent (e.g., an antibody or a bispecific agent) in a human patient that comprise administering to the patient the MET-binding agent using an intermittent dosing regimen.

The choice of delivery method for the initial and subsequent doses is made according to the ability of the animal or human patient to tolerate introduction of the MET-binding agent into the body. Thus, in any of the aspects and/or embodiments described herein, the administration of the MET-binding agent (e.g., an antibody or a bispecific agent) may be by intravenous injection or intravenously. In some embodiments, the administration is by intravenous infusion. In any of the aspects and/or embodiments described herein, the administration of the MET-binding agent may be by a non-intravenous route.

V. Kits Comprising Met/Wnt-Binding Agents

The present invention provides kits that comprise the MET-binding agents (e.g., antibodies or bispecific agents) described herein and that can be used to perform the methods described herein. In certain embodiments, a kit comprises at least one purified antibody against MET or at least one purified bispecific agent that binds MET and one or more components of the WNT pathway in one or more containers. In some embodiments, the kits contain all of the components necessary and/or sufficient to perform a detection assay, including all controls, directions for performing assays, and any necessary software for analysis and presentation of results. One skilled in the art will readily recognize that the disclosed MET-binding agents of the present invention can be readily incorporated into one of the established kit formats which are well known in the art.

Further provided are kits comprising a MET-binding agent (e.g., an antibody or bispecific agent), as well as at least one additional therapeutic agent. In certain embodiments, the second (or more) therapeutic agent is a chemotherapeutic agent. In certain embodiments, the second (or more) therapeutic agent is an angiogenesis inhibitor.

Embodiments of the present disclosure can be further defined by reference to the following non-limiting examples,

which describe in detail preparation of certain antibodies of the present disclosure and methods for using antibodies of the present disclosure. It will be apparent to those skilled in the art that many modifications, both to materials and methods, may be practiced without departing from the scope of the present disclosure.

EXEMPLARY EMBODIMENTS

Embodiment 1. A bispecific agent comprising: a) a first binding site that specifically binds human MET, and b) a second binding site that specifically binds one or more components of the WNT pathway.

Embodiment 2. The bispecific agent of embodiment 1, wherein the first binding site comprises an antigen-binding site of an antibody that specifically binds human MET.

Embodiment 3. The bispecific agent of embodiment 1 or embodiment 2, wherein the first binding site comprises a heavy chain CDR1 comprising ASYAWS (SEQ ID NO:1), a heavy chain CDR2 comprising YISYSGGTDYNPSLKS (SEQ ID NO:2), and a heavy chain CDR3 comprising KGAY (SEQ ID NO:3); and a light chain CDR1 comprising SASSS-VSSSYLY (SEQ ID NO:4), a light chain CDR2 comprising STSNLAS (SEQ ID NO:5), and a light chain CDR3 comprising HQWSSYPYT (SEQ ID NO:6).

Embodiment 4. The bispecific agent of any one of embodiments 1-3, wherein the second binding site comprises an antigen-binding site of an antibody that specifically binds one or more components of the WNT pathway.

Embodiment 5. The bispecific agent of any one of embodiments 1-4, which is a bispecific antibody.

Embodiment 6. The bispecific agent of any one of embodiments 1-5, wherein the second binding site specifically binds one or more human WNT proteins.

Embodiment 7. The bispecific agent of embodiment 6, wherein the one or more WNT proteins is selected from the group consisting of: WNT1, WNT2, WNT2b, WNT3, WNT3a, WNT7a, WNT7b, WNT8a, WNT8b, WNT10a, and WNT100b.

Embodiment 8. The bispecific agent of any one of embodiments 1-5, wherein the second binding site specifically binds one or more Frizzled (FZD) proteins.

Embodiment 9. The bispecific agent of embodiment 8, wherein the second binding site specifically binds one or more FZD proteins selected from the group consisting of: FZD1, FZD2, FZD5, FZD7, and FZD8.

Embodiment 10. The bispecific agent of any one of embodiments 1, 2, 3, 6, or 7, which comprises a soluble FZD receptor.

Embodiment 11. The bispecific agent of embodiment 10, wherein the soluble receptor comprises a Fri domain of a human FZD protein.

Embodiment 12. The bispecific agent of embodiment 10, wherein the human FZD protein is human FZD8.

Embodiment 13. The bispecific agent of embodiment 11, wherein the Fri domain of the human FZD protein comprises a sequence selected from the group consisting of: SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, and SEQ ID NO:41.

Embodiment 14. The bispecific agent of embodiment 13, wherein the Fri domain of the human FZD protein comprises SEQ ID NO:28, SEQ ID NO:29, or SEQ ID NO:39.

Embodiment 15. The bispecific agent of any one of embodiments 10-14, wherein the Fri domain of the human FZD protein is directly linked to a heterologous polypeptide.

Embodiment 16. The bispecific agent of any one of embodiments 10-14, wherein the Fri domain of the human FZD protein is connected to a heterologous polypeptide by a linker.

Embodiment 17. The bispecific agent of embodiment 15 or embodiment 16, wherein the heterologous polypeptide comprises a human Fc region.

Embodiment 18. The bispecific agent of any one of embodiments 15-17, wherein the heterologous polypeptide comprises SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:91, or SEQ ID NO:92.

Embodiment 19. The bispecific agent of embodiment 10, wherein the soluble FZD receptor comprises: (a) a first polypeptide consisting essentially of SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, or SEQ ID NO:41; and (b) a second polypeptide comprising SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, or SEQ ID NO:52; wherein the first polypeptide is directly linked to the second polypeptide.

Embodiment 20. The bispecific agent of embodiment 10, wherein the soluble FZD receptor comprises: (a) a first polypeptide comprising SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, or SEQ ID NO:41; and (b) a second polypeptide comprising SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, or SEQ ID NO:52; wherein the first polypeptide is connected to the second polypeptide by a linker.

Embodiment 21. The bispecific agent of embodiment 19 or embodiment 20, wherein the first polypeptide consists of SEQ ID NO:28.

Embodiment 22. The bispecific agent of embodiment 21, wherein the second polypeptide consists of SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, or SEQ ID NO:52.

Embodiment 23. The bispecific agent of embodiment 19 or embodiment 20, wherein the first polypeptide consists of SEQ ID NO:29.

Embodiment 24. The bispecific agent embodiment 23, wherein the second polypeptide consists of SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, or SEQ ID NO:52.

Embodiment 25. The bispecific agent of embodiment 10, wherein the soluble FZD receptor comprises SEQ ID NO:53 or SEQ ID NO:56.

Embodiment 26. The bispecific agent of embodiment 10, wherein the soluble FZD receptor comprises SEQ ID NO:56.

Embodiment 27. A bispecific agent of any one of embodiments 1-26, wherein the first binding site comprises a heavy

chain variable region having at least about 90% sequence identity to SEQ ID NO:7 and a light chain variable region having at least about 90% sequence identity to SEQ ID NO:8.

Embodiment 28. The bispecific agent of embodiment 27, wherein the first binding site comprises a heavy chain variable region having at least 95% sequence identity to SEQ ID NO:7 and a light chain variable regions have at least 95% sequence identity to SEQ ID NO:8.

Embodiment 29. The bispecific agent of embodiment 27, wherein the first antigen-binding site comprises a heavy chain variable region comprising SEQ ID NO:7 and a light chain variable region comprising SEQ ID NO:8.

Embodiment 30. The bispecific agent of any one of embodiments 1-29, which comprises a first CH3 domain and a second CH3 domain, each of which is modified to promote formation of heterodimers.

Embodiment 31. The bispecific agent of embodiment 30, wherein the first and second CH3 domains are modified based upon electrostatic effects.

Embodiment 32. The bispecific agent of any one of embodiments 1-31, which comprises a first human IgG2 constant region with amino acid substitutions at positions corresponding to positions 249 and 288 of SEQ ID NO:75, wherein the amino acids are replaced with glutamate or aspartate, and a second human IgG2 constant region with amino acid substitutions at positions corresponding to positions 236 and 278 of SEQ ID NO:75, wherein the amino acids are replaced with lysine.

Embodiment 33. The bispecific agent according to any one of embodiments 1-31, which comprises a first human IgG2 constant region with amino acid substitutions at positions corresponding to positions 236 and 278 of SEQ ID NO:75, wherein the amino acids are replaced with lysine, and a second human IgG2 constant region with amino acid substitutions at positions corresponding to positions 249 and 288 of SEQ ID NO:75, wherein the amino acids are replaced with glutamate or aspartate.

Embodiment 34. The bispecific agent of embodiment 30, wherein the first and second CH3 domains are modified using a knobs-into-holes technique.

Embodiment 35. A bispecific agent that specifically binds human MET and specifically binds one or more components of the WNT pathway, which comprises a heavy chain of SEQ ID NO:13 and a light chain of SEQ ID NO: 14.

Embodiment 36. The bispecific agent of any one of embodiments 1-35, which binds human MET with a K_D of about 100 nM or less and binds one or more components of the WNT pathway with a K_D of about 100 nM or less.

Embodiment 37. A bispecific agent which is 315B6.

Embodiment 38. The bispecific agent of any one of embodiments 1-37, which inhibits binding of MET to hepatocyte growth factor.

Embodiment 39. The bispecific agent of any one of embodiments 1-38, which facilitates internalization of MET.

Embodiment 40. The bispecific agent of any one of embodiments 1-39, which stimulates degradation of MET.

Embodiment 41. The bispecific agent of any one of embodiments 1-38, which inhibits dimerization of MET.

Embodiment 42. The bispecific agent of any one of embodiments 1-41, which inhibits activation of MET.

Embodiment 43. The bispecific agent of any one of embodiments 1-42, which inhibits binding of one or more WNT proteins to at least one FZD.

Embodiment 44. The bispecific agent of embodiment 43, wherein the FZD is selected from the group consisting of FZD1, FZD2, FZD5, FZD7, and FZD8.

Embodiment 45. The bispecific agent of embodiment 44, wherein the FZD is FZD8.

Embodiment 46. The bispecific agent of any one of embodiments 1-45, which inhibits WNT signaling.

Embodiment 47. The bispecific agent of any one of embodiments 1-46, which inhibits canonical WNT signaling.

Embodiment 48. The bispecific agent of any one of embodiments 1-47, which inhibits the growth of a tumor or tumor cells.

Embodiment 49. The bispecific agent of any one of embodiments 1-48, which induces expression of differentiation markers in a tumor.

Embodiment 50. The bispecific agent of any one of embodiments 1-49, which induces cells in a tumor to differentiate.

Embodiment 51. The bispecific agent of any one of embodiments 1-50, which reduces the frequency of cancer stem cells in a tumor.

Embodiment 52. The bispecific agent of any one of embodiments 1-51, which inhibits epithelial-mesenchymal transition (EMT).

Embodiment 53. An isolated antibody that specifically binds human MET, which comprises: a heavy chain CDR comprising ASYAWS (SEQ ID NO:1), a heavy chain CDR2 comprising YISYSGGTDYNPSLKS (SEQ ID NO:2), and a heavy chain CDR3 comprising KGAY (SEQ ID NO:3); and a light chain CDR1 comprising SASSSVSSSYLY (SEQ ID NO:4), a light chain CDR2 comprising STSNLAS (SEQ ID NO:5), and a light chain CDR3 comprising HQWSSYPYT (SEQ ID NO:6).

Embodiment 54. An isolated antibody that specifically binds human MET, which comprises: (a) a heavy chain variable region having at least about 90% sequence identity to SEQ ID NO:7; and (b) a light chain variable region having at least about 90% sequence identity to SEQ ID NO:8.

Embodiment 55. The antibody of embodiment 54, which comprises: (a) a heavy chain variable region having at least about 95% sequence identity to SEQ ID NO:7; and (b) a light chain variable region having at least about 95% sequence identity to SEQ ID NO:8.

Embodiment 56. The antibody of embodiment 54, which comprises: (a) a heavy chain variable region comprising SEQ ID NO:7; and (b) a light chain variable region comprising SEQ ID NO:8.

Embodiment 57. An isolated antibody that specifically binds human MET, which comprises: (a) a heavy chain comprising SEQ ID NO:12; and (b) a light chain comprising SEQ ID NO:14.

Embodiment 58. The antibody of any one of embodiments 53-57, which is a monoclonal antibody, a recombinant antibody, a monovalent antibody, a chimeric antibody, a humanized antibody, a human antibody, a bispecific antibody, an IgG1 antibody, an IgG2 antibody, or antibody fragment comprising an antigen-binding site.

Embodiment 59. The antibody of any one of embodiments 53-57, which is a monovalent antibody.

Embodiment 60. The antibody of any one of embodiments 53-57, which is a bispecific antibody.

Embodiment 61. The antibody of any one of embodiments 53-60, which inhibits binding of MET to hepatocyte growth factor.

Embodiment 62. A polypeptide comprising a sequence selected from the group consisting of: SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:87, and SEQ ID NO:88.

Embodiment 63. A cell comprising the bispecific agent, antibody, or polypeptide of any one of embodiments 1-62.

Embodiment 64. A cell producing the bispecific agent, antibody, or polypeptide of any one of embodiments 1-62.

Embodiment 65. An isolated polynucleotide molecule comprising a polynucleotide that encodes a bispecific agent, antibody, or polypeptide of any one of embodiments 1-62.

Embodiment 66. An isolated polynucleotide molecule comprising a polynucleotide sequence selected from the group consisting of: SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:89, and SEQ ID NO:90.

Embodiment 67. A vector comprising the polynucleotide of embodiment 65 or embodiment 66.

Embodiment 68. A cell comprising the polynucleotide of embodiment 65 or embodiment 66 or the vector of embodiment 67.

Embodiment 69. A pharmaceutical composition comprising the bispecific agent or antibody of any one of embodiments 1-61 and a pharmaceutically acceptable carrier.

Embodiment 70. A method of inhibiting growth of a tumor, wherein the method comprises contacting the tumor with an effective amount of a bispecific agent of any one of embodiments 1-52 or an antibody of any one of embodiments 53-61.

Embodiment 71. A method of inhibiting growth of a tumor in a subject, comprising administering to the subject a therapeutically effective amount of a bispecific agent of any one of embodiments 1-52 or an antibody of any one of embodiments 53-61.

Embodiment 72. A method of reducing the frequency of cancer stem cells in a tumor in a subject, comprising administering to the subject a therapeutically effective amount of a bispecific agent of any one of embodiments 1-52 or an antibody of any one of embodiments 53-61.

Embodiment 73. A method of inhibiting EMT in a tumor in a subject, comprising administering to the subject a therapeutically effective amount of a bispecific agent of any one of embodiments 1-52 or an antibody of any one of embodiments 53-61.

Embodiment 74. A method of inhibiting angiogenesis in a subject, comprising administering to the subject a therapeutically effective amount of a bispecific agent of any one of embodiments 1-52 or an antibody of any one of embodiments 53-61.

Embodiment 75. The method of embodiment 74, wherein the angiogenesis is tumor angiogenesis.

Embodiment 76. The method of any one of embodiments 70-75, wherein the tumor is selected from the group consisting of colorectal tumor, colon tumor, ovarian tumor, pancreatic tumor, lung tumor, liver tumor, breast tumor, kidney tumor, prostate tumor, gastrointestinal tumor, melanoma, cervical tumor, bladder tumor, glioblastoma, and head and neck tumor.

Embodiment 77. A method of treating cancer in a subject, comprising administering to the subject a therapeutically effective amount of a bispecific agent of any one of embodiments 1-52 or an antibody of any one of embodiments 53-61.

Embodiment 78. The method of embodiment 77, wherein the cancer is selected from the group consisting of colorectal cancer, colon cancer, ovarian cancer, pancreatic cancer, lung cancer, liver cancer, breast cancer, kidney cancer, prostate cancer, gastrointestinal cancer, melanoma, cervical cancer, bladder cancer, glioblastoma, head and neck cancer, lymphoma and leukemia.

Embodiment 79. The method of any one of embodiments 79-78, which further comprises administering at least one additional therapeutic agent.

Embodiment 80. The method of embodiment 79, wherein the additional therapeutic agent is a chemotherapeutic agent.

Embodiment 81. The method of embodiment 79, wherein the additional therapeutic agent is a second antibody.

Embodiment 82. The method of any one of embodiments 70 or 72-81, wherein the subject is human.

Embodiment 83. A method for the production of a bispecific agent or an antibody, comprising expressing at least one polynucleotide of embodiment 65 or embodiment 66 in a cell.

Embodiment 84. The method of embodiment 83, wherein the cell is a prokaryotic cell or a eukaryotic cell.

Embodiment 85. The method of embodiment 83 or embodiment 84, further comprising isolating the bispecific agent or antibody from the cell or the cell culture supernatant.

Embodiment 86. A bispecific agent comprising (a) a first antigen-binding site that binds human MET with a K_D between about 0.1 nM and about 5.0 nM and (b) a second binding site that specifically binds one or more components of the WNT pathway with a K_D between about 0.1 nM and about 20 nM.

Embodiment 87. A pharmaceutical composition comprising the bispecific agent of embodiment 86 and a pharmaceutically acceptable carrier.

Embodiment 88. A method of treating cancer in a subject, comprising administering to the subject a therapeutically effective amount of the bispecific agent of embodiment 86.

Embodiment 89. A method of identifying a human subject for treatment with a bispecific agent that specifically binds MET and specifically binds one or more components of the WNT pathway, comprising: determining if the subject has a tumor that has an elevated expression level of MET as compared to a reference sample or a pre-determined level of MET.

Embodiment 90. A method of identifying a human subject for treatment with a bispecific agent that specifically binds MET and specifically binds one or more components of the WNT pathway, comprising: (a) obtaining a tumor sample from the subject, and (b) determining if the tumor has an elevated expression level of MET as compared to a reference sample or a pre-determined level of MET.

Embodiment 91. A method of identifying a human subject for treatment with a bispecific agent that specifically binds MET and specifically binds one or more components of the WNT pathway, comprising: determining if the subject has a tumor that has an elevated expression level of MET as compared to a reference sample or a pre-determined level of MET, wherein if the tumor has an elevated expression level of MET the subject is selected for treatment with the bispecific agent.

Embodiment 92. A method of identifying a human subject for treatment with a bispecific agent that specifically binds MET and specifically binds one or more components of the WNT pathway, comprising: (a) obtaining a tumor sample from the subject, and (b) determining if the tumor has an elevated expression level of MET as compared to a reference sample or a pre-determined level of MET, wherein if the tumor has an elevated expression level of MET the subject is selected for treatment with the bispecific agent.

Embodiment 93. A method of selecting a human subject for treatment with a bispecific agent that specifically binds MET and specifically binds one or more components of the WNT pathway, comprising: determining if the subject has a tumor that has an elevated expression level of MET as compared to a reference sample or a pre-determined level of MET.

Embodiment 94. A method of selecting a human subject for treatment with a bispecific agent that specifically binds MET and specifically binds one or more components of the WNT pathway, comprising: (a) obtaining a tumor sample from the subject, and (b) determining if the tumor has an elevated

expression level of MET as compared to a reference sample or a pre-determined level of MET.

Embodiment 95. A method of selecting a human subject for treatment with a bispecific agent that specifically binds MET and specifically binds one or more components of the WNT pathway, comprising: determining if the subject has a tumor that has an elevated expression level of MET as compared to a reference sample or a pre-determined level of MET, wherein if the tumor has an elevated expression level of MET the subject is selected for treatment with the bispecific agent.

Embodiment 96. A method of selecting a human subject for treatment with a bispecific agent that specifically binds MET and specifically binds one or more components of the WNT pathway, comprising: (a) obtaining a tumor sample from the subject, and (b) determining if the tumor has an elevated expression level of MET as compared to a reference sample or a pre-determined level of MET, wherein if the tumor has an elevated expression level of MET the subject is selected for treatment with the bispecific agent.

Embodiment 97. The method of any one of embodiments 89-96, wherein the bispecific agent is a bispecific agent of any one of embodiments 1-52.

Embodiment 98. The method of any one of embodiments 89-97, wherein the tumor is selected from the group consisting of colorectal tumor, colon tumor, ovarian tumor, pancreatic tumor, lung tumor, liver tumor, breast tumor, kidney tumor, prostate tumor, gastrointestinal tumor, melanoma, cervical tumor, bladder tumor, glioblastoma, and head and neck tumor.

Embodiment 99. The method of embodiment 98, wherein the tumor is a lung tumor.

Embodiment 100. The method of embodiment 98, wherein the tumor is a pancreatic tumor.

Embodiment 101. The method any one of embodiments 89-100, wherein the expression level of MET is determined in a sample by a PCR-based assay, microarray analysis, or immunohistochemistry.

Embodiment 102. The method of embodiment 101, wherein the sample is a fresh tumor sample, a frozen tumor sample, or a formalin-fixed paraffin-embedded sample.

Embodiment 103. Use of the bispecific agent of any one of embodiments 1-52 or an antibody of any one of embodiments 53-61 for the manufacture of a medicament for the treatment of cancer.

Embodiment 104. A bispecific agent or an antibody for use in a method of treating cancer, wherein the bispecific agent is a bispecific agent of any one of embodiments 1-52 or the antibody is an antibody of any one of embodiments 53-61.

EXAMPLES

Example 1

Binding Affinities of MET-Binding Agents

The K_D of monovalent version of 73R009, monovalent anti-MET antibody 5D5, and anti-MET/FZD8-Fc bispecific agent 315B6 were determined using a Biacore 2000 system from Biacore LifeSciences (GE Healthcare). A goat anti-human antibody (Invitrogen H10500) was coupled to a carboxymethyl-dextran (CM5) SPR chip using standard amine-based chemistry (NHS/EDC) and blocked with ethanolamine. Antibodies were diluted to a concentration of 10 μ g/ml in HBS-P-BSA (0.01M HEPES pH7.4, 0.15M NaCl, 0.005% v/v Polysorbate 20, 100 μ g/ml BSA) and captured onto the chip via the anti-human antibody. Human MET was serially diluted 2-fold from 300 nM to 37.5 nM in HBS-P-BSA and injected sequentially over the captured anti-MET

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antibodies. MET association and dissociation was measured at each concentration. After each antigen injection 5 μ l of 100 mM H_3PO_4 was injected to remove the antigen-antibody complex and a subsequent injection performed. Kinetic data were collected over time and were fit using the simultaneous global fit equation to yield affinity constants (K_D values) for each agent.

Bivalent "parental" antibody 73R009 had an affinity constant (K_D) for human MET of 1.1 nM, monovalent version of 73R009 had a K_D for human MET of 1.4 nM, monovalent antibody 5D5 had a K_D for human MET of 7.2 nM, and bispecific agent 315B6 had a K_D for human MET of 1.8 nM. Thus, the monovalent anti-MET antibody 73R009 and the bispecific agent 315B6 both demonstrated binding affinity very similar to the parental antibody despite the fact the parental antibody is bivalent. In addition, the bispecific agent 315B6 appeared to have stronger affinity for human MET than anti-MET antibody 5D5.

The anti-MET/FZD8-Fc bispecific agent 315B6 has been shown to not bind mouse MET.

Anti-MET/FZD8-Fc bispecific agent 315B6 comprises (a) a heavy chain encoded by the plasmid deposited with ATCC, 10801 University Boulevard, Manassas, Va., USA, under the conditions of the Budapest Treaty on Mar. 12, 2013 and assigned designation number PTA-13609, (b) a light chain encoded by the plasmid deposited with ATCC under the conditions of the Budapest Treaty on Mar. 12, 2013 and assigned designation number PTA-13610, and (c) a fusion protein encoded by the plasmid deposited with ATCC under the conditions of the Budapest Treaty on Mar. 12, 2013 and assigned designation number PTA-13611.

Example 2

Inhibition of binding of hepatocyte growth factor to MET

A full-length human MET (FL-MET) construct was generated using standard recombinant DNA techniques. HEK-293T cells were transiently transfected with the MET construct and a GFP plasmid at a plasmid MET: GFP ratio of 2:1. After 24 hours, transfected cells were harvested and suspended in ice cold PBS containing 2% FBS. The transfected cells were incubated on ice in the presence of 10, 5, 2.5, 1.25, 0.625, 0.3, or 0.16 μ g/ml of monovalent anti-MET antibody 5D5, monovalent version of anti-MET antibody 73R009, or anti-MET/FZD8-Fc bispecific agent 315B6 for 1 hour. 30 ng of hepatocyte growth factor (HGF) conjugated to biotin was added to each sample and incubated on ice for an additional 40 minutes. Cells were washed with PBS containing 2% FBS, PE-conjugated streptavidin was added, and the cells were incubated for 1 hour. Transfected cells were incubated with no HGF as a negative control and with HGF but no antibody or binding agent as a positive control. After final incubation, cells were stained with 5 μ g/ml DAPI and analyzed on a FACSCanto II instrument (BD Biosciences, San Jose, Calif.) and the data was processed using FlowJo software.

As shown in FIG. 1, the positive controls showed that approximately 20% of the transfected cells expressed MET and were bound by human HGF (FIG. 1A). Inhibition of HGF binding to MET by the binding agents was compared to the positive control of 20% binding. The monovalent anti-MET antibody 5D5 reduced binding of HGF to MET by approximately 70% at the highest concentration of 10 μ g/ml with a dose-dependent response down to a reduction of 28% at the lowest concentration of 0.16 μ g/ml (FIG. 1B). In contrast, the monovalent version of anti-MET antibody 73R009 reduced binding of HGF to MET by approximately 72% at the highest concentration of 10 μ g/ml with a dose-dependent response

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down to a reduction of approximately 56% at the lowest concentration of 0.16 μ g/ml (FIG. 1C). Similarly, the bispecific anti-MET/FZD8-Fc agent reduced binding of HGF to MET by approximately 80% at the highest concentration of 10 μ g/ml with a dose-dependent response down to a reduction of approximately 56% at the lowest concentration of 0.16 μ g/ml (FIG. 1D).

These results showed that both the monovalent version of anti-MET antibody 73R009 and the bispecific anti-MET/FZD8-Fc agent 315B6 were strong blockers of HGF binding to MET. In addition, both appeared to have a greater ability to block binding of HGF to MET than anti-MET antibody 5D5 and were able to block binding at lower concentrations.

Example 3

Inhibition of HGF-induced MET activity

MET activation in human cells can be characterized by analyzing MET phosphorylation and downstream activation of mitogen-activated protein kinase (MAPK) and AKT after HGF stimulation.

A549 cells were seeded into 12-well plates at 1.5×10^5 cells/well in DMEM medium containing 10% FBS and grown overnight. Cells were transferred to serum-free medium and after approximately 18 hours the cells were pre-treated for one hour with monovalent version of anti-MET antibody 73R009, bispecific anti-MET/FZD8-Fc agent 5D5/FZD, and bispecific anti-MET/FZD8-Fc agent 315B6 at concentrations of 50, 10, 2, and 0.4 μ g/ml. Subsequently the cells were stimulated with 50 ng/ml human HGF (EMD Millipore, Billerica Mass.) for 15 minutes. Cells were lysed and cell lysate supernatants were collected. Cell lysates were resolved by SDS-PAGE using 4-12% NuPAGE Novex gels (Invitrogen/Life Technologies, Grand Island, N.Y.), transferred to nitrocellulose membranes, and analyzed by Western blot techniques. Antibodies used were anti-human MET (anti-Met (L41G3) mAb, Cell Signaling Technology, Danvers, Mass.); anti-phospho-MET (anti-phospho-MET (Tyr1234/1235) mAb, Cell Signaling Technology, Danvers, Mass.); anti-phospho-AKT (anti-phospho-AKT (Ser473) mAb, Cell Signaling Technology, Danvers, Mass.); anti-phospho-MAPK (anti-phospho-p44/42 MAPK (Erk1/2) (Thr202/Tyr204), Cell Signaling Technology, Danvers, Mass.); and anti-actin (anti-beta actin antibody, Abcam, Cambridge, Mass.).

As shown in FIG. 2, bispecific anti-MET/FZD8-Fc agent 315B6 reduced the amount of phosphorylated MET to a greater extent than the bispecific anti-MET/FZD agent 5D5/FZD or the monovalent version of anti-MET antibody 73R009. At the highest concentration, it appeared that 315B6 reduced the amount of phosphorylated AKT to a greater extent than the other agents also. These studies demonstrated that the bispecific anti-MET/FZD8-Fc agent 315B6 was able to inhibit and/or block HGF-induced MET activation and was able to inhibit and/or block MET activation to a greater extent than the bispecific anti-MET/FZD agent 5D5/FZD or the monovalent version of anti-MET antibody 73R009.

Example 4

Inhibition of WNT Signaling

STF-293 cells were cultured in DMEM supplemented with antibiotics and 10% FCS. The STF-293 cells are HEK-293 cells stably integrated with an 8 \times TCF Luc reporter vector and a *Renilla* luciferase reporter. The 8 \times TCF Luc reporter contains seven copies of the TCF binding site linked to a promoter upstream of a firefly luciferase reporter gene to mea-

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sure canonical WNT signaling levels (Gazit et al., 1999, Oncogene 18:5959-66). The *Renilla* luciferase reporter (Promega; Madison, Wis.) is used as an internal control for transfection efficiency. Anti-MET/FZD bispecific agent 315B6 and control agents anti-MET monovalent agent 5D5/FLAG and monovalent agent FZD8/FLAG were serially diluted 5-fold from 20 ug/ml to 0.0064 ug/ml, added to the appropriate wells, and incubated overnight. The cells were then incubated in the presence or absence of WNT3A-conditioned medium that had been prepared from L cells that stably express WNT3a or control conditioned media from L cells not over-expressing WNT3A. After overnight incubation, luciferase levels were measured using a dual luciferase assay kit (Promega; Madison, Wis.) with firefly luciferase activity normalized to *Renilla* luciferase activity.

As shown in FIG. 3, anti-MET/FZD8-Fc bispecific agent 315B6 inhibited WNT pathway signaling. The inhibition was similar to the monovalent FZD8/FLAG agent and as expected the anti-MET 5D5/FLAG agent had no ability to inhibit WNT pathway signaling. Thus, in combination with the results presented in Example 3, the anti-MET/FZD8-Fc bispecific agent 315B6 has demonstrated the ability to inhibit both MET-induced and WNT-induced signaling and/or activation.

Example 5

Inhibition of Lung Tumor Growth In Vivo

OMP-LU45 tumors were selected based on the high level of MET expression observed in microarray analysis. Dissociated OMP-LU45 lung tumor cells (1×10^5 cells) were injected in to 6-8 week old NOD/SCID mice. Tumors were allowed to grow for 26 days until they reached an average volume of 90 mm^3 . The mice were randomized (n=10 per

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group) and treated with a monovalent anti-MET antibody (5D5/FLAG), a control antibody, a monovalent FZD8-Fc (FZD8Fc/FLAG), a bivalent FZD8-Fc (54F28), or an anti-MET/FZD8Fc bispecific agent, either as single agents or in combination with taxol. Protein agents were dosed at 25 mg/kg once a week, and taxol was dosed at 15 mg/ml once a week. Administration of the protein agents and taxol was performed via injection into the intraperitoneal cavity. Tumor growth was monitored and tumor volumes were measured with electronic calipers at the indicated time points. Data are expressed as mean \pm S.E.M.

When used as a monotherapy, all of the agents had minimal or no detectable effect on LU45 tumor growth as compared to the control antibody (FIG. 4A). In contrast, the MET/FZD8-Fc bispecific agent in combination with taxol significantly inhibited OMP-LU45 tumor growth and this inhibition of tumor growth was greater than inhibition observed with any of the other agents in combination with taxol (FIG. 4B).

It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application.

All publications, patents, patent applications, internet sites, and accession numbers/database sequences including both polynucleotide and polypeptide sequences cited herein are hereby incorporated by reference herein in their entirety for all purposes to the same extent as if each individual publication, patent, patent application, internet site, or accession number/database sequence was specifically and individually indicated to be so incorporated by reference.

Following are the sequences disclosed in the application:

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73R009 Heavy chain CDR1
(SEQ ID NO: 1)
ASYAWS

73R009 Heavy chain CDR2
(SEQ ID NO: 2)
YISYSGGTDYNPSLKS

73R009 Heavy chain CDR3
(SEQ ID NO: 3)
KGAY

73R009 Light chain CDR1
(SEQ ID NO: 4)
SASSSVSSSYLY

73R009 Light chain CDR2
(SEQ ID NO: 5)
STSNLAS

73R009 Light chain CDR3
(SEQ ID NO: 6)
HQWSSYPYT

73R009 Heavy chain variable region amino acid sequence
(SEQ ID NO: 7)
QVQLQESGPGLVKPSSETLSLTCTVTGTTITASYAWSWIRQPPGKGLEWMGYISYSGGTDY
NPSLKSRTISRDTFKNQFSLKLSVTAADTATYYCARKGAYWGQGLVTVSS

73R009 Light chain variable region amino acid sequence
(SEQ ID NO: 8)
DIVLTQSPATLSASPGKVTLTCSASSSVSSSYLYWYQQKPGAPKLLIYSTSNLASGVP
ARFSGSGSGTSYSLTISSELEPFDATYYCHQWSSYPYTEGGGKLEIK

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-continued

73R009 Heavy chain amino acid sequence with predicted signal sequence underlined

(SEQ ID NO: 9)

MKHLWFFLLLVAAAPRWLSQVQLQESGPGLVKPSSETLSLTCTVTGTTITASYAWSWIRQP

PGKGLEWMGYISYSGGTDYNPSLKSRTISRDTFKNQFSLKLSVTAADTATYYCARKGA

YWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTS

GVHTFPAVLQSSGLYSLSSVTVPSNFGTQTYTCNVDHKPSNTKVDKTVKCCVECP

CPAPPVAGPSVFLEPPKPKDTLMISRTPPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKT

KPREEQFNSTFRVSVLTVVHQDWLNGKEYCKVSNKGLPAPIEKTISKTKGQPREPQVY

TLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPMLDSGDSFFLYSK

LTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGK

73R009 (13A variant) Heavy chain amino acid sequence with predicted signal sequence underlined

(SEQ ID NO: 10)

MKHLWEELLLVAAAPRWLSQVQLQESGPGLVKPSSETLSLTCTVTGTTITASYAWSWIRQP

PGKGLEWMGYISYSGGTDYNPSLKSRTISRDTFKNQFSLKLSVTAADTATYYCARKGA

YWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTS

GVHTFPAVLQSSGLYSLSSVTVPSNFGTQTYTCNVDHKPSNTKVDKTVKCCVECP

CPAPPVAGPSVFLFPPKPKDTLMISRTPPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKT

KPREEQFNSTERVSVLTVVHQDWLNGKEYCKVSNKGLPAPIEKTISKTKGQPREPQVY

TLPPSREKMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPMLKSDGDSFFLYSK

LTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGK

738009 Light chain amino acid sequence with predicted signal sequence underlined

(SEQ ID NO: 11)

MKHLWFFLLLVAAAPRWLSDIVLTQSPATLSASPGKVTLTCSASSSVSSSYLYWYQQK

PGAPKLLIYSTNLSAGVPARFSGSGTSYSLTISLSEPEDFATYYCHQWSSYPYTFPG

GTKLEIKRTVAAPSFIFFPSDEQLKSGTASVVCLLMIFYPREAKVQKVDNALQSGNSQ

ESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

73R009 Heavy chain amino acid sequence without predicted signal sequence

(SEQ ID NO: 12)

QVQLQESGPGLVKPSSETLSLTCTVTGTTITASYAWSWIRQPPGKGLEWMGYISYSGGTDY

NPSLKSRTISRDTFKNQFSLKLSVTAADTATYYCARKGAYWGQGTLVTVSSASTKGPS

VFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSS

VTVPSNFGTQTYTCNVDHKPSNTKVDKTVKCCVECP

CPAPPVAGPSVFLEPPKPKDTLMISRTPPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKT

KPREEQFNSTERVSVLTVVHQDWLNGKEYCKVSNKGLPAPIEKTISKTKGQPREPQVY

TLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPMLDSGDSFFLYSK

LTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGK

73R009 (13A variant) Heavy chain amino acid sequence without predicted signal sequence

(SEQ ID NO: 13)

QVQLQESGPGLVKPSSETLSLTCTVTGTTITASYAWSWIRQPPGKGLEWMGYISYSGGTDY

NPSLKSRTISRDTFKNQFSLKLSVTAADTATYYCARKGAYWGQGTLVTVSSASTKGPS

VFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSS

VTVPSNFGTQTYTCNVDHKPSNTKVDKTVKCCVECP

CPAPPVAGPSVFLEPPKPKDTLMISRTPPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKT

KPREEQFNSTFRVSVLTVVHQDWLNGKEYCKVSNKGLPAPIEKTISKTKGQPREPQVY

-continued

VHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREKMTKNQVSLTCL
 VKGFYPSDIAVEWESNGQPENNYKTTTPMLKSDGSFELYSKLTVDKSRWQQGNVESCSVM
 HEALHNHYTQKSLSLSPGK

73R009 Light chain amino acid sequence without predicted signal
 sequence

(SEQ ID NO: 14)

DIVLTQSPATLSASPEKVTLTCSASSVSSSYLYWYQQKPGQAPKLLIYSTNLSGV
 ARFSGSGSGTSYSLTISLEPEDFATYYCHQWSSYPYTFGGGTGLEIKRTVAAPSVFIFP
 PSDEQLKSGTASVVCLLNNEYPREAKVQWKVDNALQSGNSQESVTEQDSKDSSTYSLSSTL
 TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

73R009 Heavy chain nucleotide sequence

(SEQ ID NO: 15)

ATGAAGCATCTGTGGTTTTTCTCTGCTGCTCGTGGCTGCTCCCGGTGGGTCTGTCTCAG
 GTCCAATTGCAAGAGTCAGGACCAGGGCTTGTGAAGCCCTCAGAGACTCTGTCACTCACT
 TGTACCGTGACCGGAACACCATCACTGCCTCTACGCCTGGAGCTGGATCAGGCAGCCT
 CCGGAAAAGGCCTGGAATGGATGGGTACATCTCTTATTCAGGCGGAACCGACTACAAT
 CCTAGCCTGAAGTCTCGCATCACCATTTACGCGATACCTTCAAGAACCAATTAGCCTT
 AAATCTCTCCAGCGTGACCGCTGCAGACACTGCCACCTACTACTGCGCAAGAAAGGGAGCC
 TATTGGGGTCAGGGGACCCCTTGTGACCGTGAGCTCAGCCTCTACCAAGGGCCCTAGCGTC
 TTCCCTCTGGCCCCCTGCTCCCGGTCCACCAGCGAGAGCACAGCCGCCCTGGGCTGCCTG
 GTCAAGGACTACTTCCCCGAACCTGTGACAGTGTCTTGAAGTCCGGCGCTCTGACCAGC
 GGCGTGACACCTTCCCAGCTGTCTCCAGTCTCTCCGACTCTACTCCCTCTCCTCCGTG
 GTGACAGTGCCTCTCCAATTCCGGCACCCAGACCTACACCTGCAACGTCGATCACAAG
 CCCAGCAACACCAAGGTTGATAAGACAGTTGAGCGCAAATGTTGTGTCGAGTGCCCTCCT
 TGCCAGCCCCCTCTGTGGCTGGACCTTCCGTCTTCTCTTCCCCCTAAACCCAAAGAC
 ACCCTCATGATCTCCCGGACCCCTGAGGTACATGCGTGGTGGTGGAGCTGAGCCACGAA
 GACCCCGAGGTCCAGTTCAACTGGTATGTGGACGGCGTGGAGGTGCATAATGCCAAGACA
 AAGCCACGGGAGGAGCAGTTCAACAGCACATTCCGGGTGGTCAGCGTCTCACCCTTGTG
 CACCGAGTGGCTGAACGGCAAGGAGTACAAGTGCAAAGTCTCAACAAAGGCCTCCCT
 GCCCCATCGAGAAAACCATCTCCAAAACCAAGGGCAGCCAGGGAACACAGGTGTAC
 ACCCTGCCCCCTTCCCGGAGGARATGACCAAGAACAAGTCAGCCTGACCTGCCTGGTC
 AAAGGCTTCTACCCCTCCGACATCGCCGTGGAGTGGGAGAGCAATGCGCAGCCTGAGAAC
 AACTACAAGACCACACCTCCCATGCTGGAYTCGACGGCTCCTTCTTCTCTACTCCAAA
 CTCACCGTGGACAAGAGCAGGTGGCAGCAGGGAACGTCTTCTCTGCTCCGTGATGCAT
 GAGGCTCTGCACAACCACTACACACAGAAGTCCCTCTCCCTGTCTCCTGGAAAA

Wherein R = A or G

Wherein Y = C or T

73R009 (13A variant) Heavy chain nucleotide sequence

(SEQ ID NO: 16)

ATGAAGCATCTGTGGTTTTTCTCTGCTGCTCGTGGCTGCTCCCGGTGGGTCTGTCTCAG
 GTCCAATTGCAAGAGTCAGGACCAGGGCTTGTGAAGCCCTCAGAGACTCTGTCACTCACT
 TGTACCGTGACCGGAACACCATCACTGCCTCTACGCCTGGAGCTGGATCAGGCAGCCT
 CCGGAAAAGGCCTGGAATGGATGGGTACATCTCTTATTCAGGCGGAACCGACTACAAT
 CCTAGCCTGAAGTCTCGCATCACCATTTACGCGATACCTTCAAGAACCAATTAGCCTT

-continued

AAACTCTCCAGCGTGACCGCTGCAGACACTGCCACCTACTACTGCGCAAGAAAGGGAGCC
 TATTGGGGTCAGGGGACCCCTTGAGACCGTGAGCTCAGCCTCTACCAAGGGCCCTAGCGTG
 TTCCCTCTGGCCCCCTGCTCCCGGTCCACCAGCGAGAGCACAGCCGCCCTGGGCTGCCTG
 GTCAAGGACTACTTCCCCGAACCTGTGACAGTGTCTGGAACCTCCGGCGCTCTGACCAGC
 GGCGTGACACACCTTCCCAGCTGTCTCCAGTCTCCGGACTCTACTCCCTCTCCTCCGTG
 GTGACAGTGCCCTCTCCAACCTTCGGCACCCAGACCTACACCTGCAACGTGATCACAAG
 CCCAGCAACACCAAGGTTGATAAGACAGTTGAGCGCAAATGTTGTGTCGAGTGCCCTCCT
 TGCCAGCCCCCTCCTGTGGCTGGACCTTCCGTCTTCTCTTCCCCCTAAACCCAAAGAC
 ACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAA
 GACCCCGAGGTCCAGTTCAACTGGTATGTGGACGGCGTGGAGGTGCATAATGCCAAGACA
 AAGCCACGGGAGGAGCAGTTCAACAGCACATTCCGGGTGGTCAGCGTCTCACCCTGTGT
 CACCGAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAAGTCTCCAACAAAGGCCTCCCT
 GCCCCATCGAGAAAACCATCTCCAAAACCAAAGGGCAGCCAGGGAACACAGGTGTAC
 ACCCTGCCCCCTTCCCGGGAGAAGATGACCAAGAACCAAGTCAGCCTGACCTGCCTGGTC
 AAAGGCTTCTACCCCTCCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCTGAGAAC
 AACTACAAGACCACACCTCCCATGCTGAAGTCCGACGGCTCCTTCTTCTCTACTCCAAA
 CTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCTGCTCCGTGATGCAT
 GAGGCTCTGCACAACCACTACACACAGAAGTCCCTCTCCCTGTCTCCTGGAAAA

73R009 Heavy chain nucleotide sequence without predicted signal sequence

(SEQ ID NO: 17)

CAGGTCCAATTGCAAGAGTCAGGACCAGGGCTTGTAAGCCCTCAGAGACTCTGTCACTC
 ACTTGTAACCGTGACCGGAACTACCATCACTGCCTCCTACGCCTGGAGCTGGATCAGGCAG
 CCTCCGGGAAAAGGCTGGAATGGATGGGTACATCTCCTATTACGGCGGAACCGACTAC
 AATCCTAGCCTGAAGTCTCGCATCACCATTTCACGCGATACCTTCAAGAACCAATTGAGC
 CTTAAACTCTCCAGCGTGACCGCTGCAGACACTGCCACCTACTACTGCGCAAGAAAGGGA
 GCCTATTGGGGTCAGGGGACCCCTTGAGACCGTGAGCTCAGCCTCTACCAAGGGCCCTAGC
 GTCTTCCCTCTGGCCCCCTGCTCCCGGTCCACCAGCGAGAGCACAGCCGCCCTGGGCTGC
 CTGGTCAAGGACTACTTCCCCGAACCTGTGACAGTGTCTGGAACCTCCGGCGCTCTGACC
 AGCGGCGTGACACACCTTCCCAGCTGTCTCCAGTCTCCGGACTCTACTCCCTCTCCTCC
 GTGGTGACAGTGCCCTCTCCAACCTTCGGCACCCAGACCTACACCTGCAACGTGATCAC
 AAGCCCAGCAACACCAAGGTTGATAAGACAGTTGAGCGCAAATGTTGTGTCGAGTGCCCT
 CCTTGCCAGCCCCCTCCTGTGGCTGGACCTTCCGTCTTCTCTTCCCCCTAAACCCAAA
 GACACCCCTCATGATCTCCCGGACCCCTGAGGTACATGCGTGGTGGTGGACGTGAGCCAC
 GAAGACCCCGAGGTCCAGTTCAACTGGTATGTGGACGGCGTGGAGGTGCATAATGCCAAG
 ACAAGCCACGGGAGGAGCAGTTCAACAGCACATTCCGGGTGGTCAGCGTCTCACCCTGT
 GTGACACGAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAAGTCTCCAACAAAGGCCTC
 CCTGCCCCCATCGAGAAAACCATCTCCAAAACCAAAGGGCAGCCAGGGAACACAGGTG
 TACACCTGCCCCCTTCCCGGGAGGARATGACCAAGAACCAAGTCAGCCTGACCTGCCTG
 GTCAAGGCTTCTACCCCTCCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCTGAG

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AACAAC TACAAG ACCACACCTCCCATGCTGGAYTCCGACGGCTCCTTCTCCTCTACTCC
AAACTCACC GTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCCTGCTCCGTGATG
CATGAGGCTCIGCACAACCACTACACACAGAAGTCCCTCTCCCTGTCTCCTGGAAAA

Wherein R = A or G
Wherein Y = C or T

73R009 (13A variant) Heavy chain nucleotide sequence without
predicted signal sequence

(SEQ ID NO: 18)

CAGGTCCAATTGCAAGAGTCAGGACCAGGGCTTGTGAAGCCCTCAGAGACTCTGTCACTC
ACTTGTACCGTGACCGGAAC TACCATCACTGCCTCTACGCTGGAGCTGGATCAGGCAG
CCTCCGGGAAAAGGCTGGAATGGATGGGTACATCTCCTATT CAGGCGGAACCGACTAC
AATCTAGCCTGAAGTCTCGCATCACCATTTCACGCGATACCTTCAAGAACCAATT CAGC
CTTAAACTCTCCAGCGTGACCGCTGCAGACACTGCCACCTACTACTGCGCAAGAAAGGGA
GCCTATTGGGGTCAGGGGACCCTTGTGACCGTGAGCTCAGCCTCTACCAAGGGCCCTAGC
GTCTTCCCTCTGGCCCCCTGCTCCCGGTCCACCAGCGAGAGCACAGCCGCCCTGGGCTGC
CTGGTCAAGGACTACTTCCCCGAACCTGTGACAGTGTCTGGAATCCGGCGCTCTGACC
AGCGGCGTGACACCTTCCCAGCTGTCTCCAGTCTCCGACTCTACTCCCTCTCCTCC
GTGGTGACAGTGCCCTCTCCAATTTCGGCACCCAGACCTACACCTGCAACGTCGATCAC
AAGCCCAAGCAACCAAGGTTGATAAGACAGTTGAGCGCAAATGTTGTGTCGAGTGCCCT
CCTTGCCCAAGCCCTCCTGTGGCTGGACCTTCCGTCTTCTCTTCCCCCTAAACCCAAA
GACACCCTCATGATCTCCCGGACCCCTGAGGT CACATGCGTGGTGGTGGACGTGAGCCAC
GAAGACCCCGAGGTCCAGTTCAACTGGTATGTGGACGCGTGGAGGTGCATAATGCCAAG
ACAAAGCCACGGGAGGAGCAGTTCAACAGCACATTCCGGGTGGTCAGCGTCCTCACC GTT
GTGCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAAGTCTCAACAAAGGCCTC
CCTGCCCCATCGAGAAAACCATCTCCAAAACCAAGGGCAGCCAGGGAACCAAGGTG
TACACCCTGCCCCCTTCCCGGAGAAGATGACCAAGAACCAAGTCAGCCTGACCTGCCTG
GTCAAAGGCTTCTACCCCTCCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCTGAG
AACAAC TACAAG ACCACACCTCCCATGCTGAAGTCCGACGGCTCCTTCTCCTCTACTCC
AAACTCACC GTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCCTGCTCCGTGATG
CATGAGGCTCTGCACAACCACTACACACAGAAGTCCCTCTCCCTGTCTCCTGGAAAA

73R009 Light chain nucleotide sequence

(SEQ ID NO: 19)

ATGAAGCACCTCTGGTTCTTCTTCTTCTTGTGGCCGCTCCCGCTGGGTCCTCAGCGAT
ATCGTGCTGACCCAGTCACCCGCCACCCTCTCAGCTTACCTGGCGAGAAGTCACTCTG
ACTTGCTCTGCCTCATCTAGCGTGTATCTTCATATCTGTACTGGTATCAGCAAAAACCG
GGACAAGCCCCGAAGCTCCTGATCTACAGCACCAAGCTTGATCCGGAGTGCCTGCC
AGGTTTAGCGGGTCCGGGTCCGGTACCTCATATTCACTGACCATTTCTTCTCTGAACCC
GAAGATTTGCTACCTACTACTGTATCAGTGGTCTAGCTACCCATACACTTTCGGCGGA
GGAACCAAACTGGAGATTAAGCGTACGGTGGCAGCCCTTCTGTCTTTATCTTCCCTCCA
TCCGACGAGCAGCTCAAATCAGGAACCGCTTCTGTGCTGTGCCTGCTTAACAATTTCTAC
CCACGGGAAGCCAAGGTGCAGTGAAGGTGGACAATGCCCTGCAATCAGGTAATTCCTCAA

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GAGTCAGTGACTGAACAGGATAGCAAGGACAGCACCTATTCACCTCTCCAGCACTCTGACC
 CTGTCCAAGGCTGACTACGAAAAGCATAAGGTGTACGCATGCGAGGTGACCCACCAGGGT
 CTGAGCAGCCCCGTACCAAGTCTTTCAACAGAGGGGAGTGT

73R009 Light chain nucleotide sequence without predicted signal
 sequence

(SEQ ID NO: 20)
 GATATCGTGCTGACCCAGTCACCCGCCACCCTCTCAGCTTCACCTGGCGAGAAGGTCACT
 CTGACTTGCTCTGCCTCATCTAGCGTGTATCTTCATATCTGTACTGGTATCAGCAAAAA
 CCGGGACAAGCCCCGAAGCTCCTGATCTACAGCACCAGCAACCTTGCATCCGGAGTGCCT
 GCCAGGTTTAGCGGGTCCGGGTCCGGTACCTCATATTCAGTACCATTCTTCTCTTGAA
 CCCGAAGATTTTCGCTACCTACTACTGTATCAGTGGTCTAGCTACCCATACACTTTCGGC
 GGAGGAACCAAAGTGGAGATTAAGCGTACGGTGGCAGCCCCCTTCTGTCTTTATCTTCCCT
 CCATCCGACGAGCAGCTCAAATCAGGAACCGCTTCTGTCTGTGCTGCTTAACAATTTC
 TACCACGGGAAGCCAAGGTGCAGTGGAAAGTGGACAATGCCCTGCAATCAGGTAATTCC
 CAAGAGTCAGTGACTGAACAGGATAGCAAGGACAGCACCTATTCACCTCTCCAGCACTCTG
 ACCCTGTCCAAGGCTGACTACGAAAAGCATAAGGTGTACGCATGCGAGGTGACCCACCAG
 GGTCTGAGCAGCCCCGTACCAAGTCTTTCAACAGAGGGGAGTGT

Human FZD1 Fri domain amino acid sequence

(SEQ ID NO: 21)
 QQPPPPQQQSGQQYNGERGISVDPHGYCQPIISIPLCDIAYNQTIMPNNLLGHTNQEDA
 GLEVHQFYPLVKVQCSAELKFPLCSMYAPVCTVLEQALPPCRSLCERARQGCEALMNKFG
 FQWPDTLKCEKFPVHGAGELCVGQNTSDKGT

Human FZD2 Fri domain amino acid sequence

(SEQ ID NO: 22)
 QFHGEKGISIPDHGFCQPIISIPLCDIAYNQTIMPNNLLGHTNQEDAGLEVHQFYPLVKVQ
 CSPELRFPLCSMYAPVCTVLEQAIPPCRSICERARQGCEALMNKFGFQWPERLRCEHFPR
 HGAEQICVGQNHSEGD

Human FZD3 Fri domain amino acid sequence

(SEQ ID NO: 23)
 HSLFSCEPITLRMCQDLPYNTTFMPNLLNHYDQQTAAALAMEFPFHPMNLDCSRDF
 RPFLCALYAPICMEYGRVTLPCRRLCQRAYSECSKLMEMFGVPWPEDECSRFPDCDEPY
 PRLVDL

Human FZD4 Fri domain amino acid sequence

(SEQ ID NO: 24)
 FGDEEERRCDPIRISMCQNLGYNVTMPNVLVGHELQTDALQLTFTPLIQYGCSSQLQF
 FLCVVYVPMCTEKINIPGPGGMCLSVKRRCEPVLKEFGFAWPESLNCSEKFPQNDHNNH
 MCMEGPGDEEV

Human FZD5 Fri domain amino acid sequence

(SEQ ID NO: 25)
 ASKAPVCQEITVPMCRGIGYNLTHMPNQFNHDTQDEAGLEVHQFWPLVEIQCSPLDRFPL
 CSMYTPICLPDYHKPLPPCRSV CERAKAGCSPLMRQYGFAPWPERMSCDRLPVLGRDAEVL
 CMDYNRSEATT

Human FZD6 Fri domain amino acid sequence

(SEQ ID NO: 26)
 HSLFTCEPITVPRCKMAYNMFTFFPNLMGHYDQSIAAVEMEHLPLANLECSNFIETFLC
 KAFVPTCIEQIHVVPPCRKLCEKVYSDCKKLIDTFGIRWPEELECDRLQYCDDETVPVTFD
 PHTEFLG

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Human FZD7 Fri domain amino acid sequence (SEQ ID NO: 27)

QPYHGEGKISVPDHGFCQPIISIPLCCTDIAYNQITILPNLLGHTNQEDAGLEVHQFYPLVKV

QCSPELRFFFLCSMYAPVCTVLDQAIPPCRSVCERARQGCEALMNKFGFQWPERLRCENFP

VHGAGEICVGQNTSDGSG

Human FZD8 Fri domain amino acid sequence (SEQ ID NO: 28)

ASAKELACQEITVPLCKGIGYNYTYMPNQFNHDTQDEAGLEVHQFWPLVEIQCSDDLKFF

LCSMYTPICLEDYKKPLPPCRSV CERAKAGCAPLMRQYGFAPWDRMRCDRLPEQGNPDTL

CMDYNRTDLTT

Human FZD8 Fri domain amino acid sequence (variant) (SEQ ID NO: 29)

ASAKELACQEITVPLCKGIGYNYTYMPNQFNHDTQDEAGLEVHQFWPLVEIQCSDDLKFF

LCSMYTPICLEDYKKPLPPCRSV CERAKAGCAPLMRQYGFAPWDRMRCDRLPEQGNPDTL

CMDYNRTDL

Human FZD9 Fri domain amino acid sequence (SEQ ID NO: 30)

LEIGRFDPERGRGAAPCQAVEIPMCRGIGYNLTRPNLLGHTSQGEAAAEAEFAPLVQY

GCHSHLRFFFLCSLYAPMCTDQVSTPIACRPMCEQARLRCAPIEQFNEGWPDSLDCARL

PTRNDPHALCMEAPENA

Human FZD10 Fri domain amino acid sequence (SEQ ID NO: 31)

ISSMDMERPGDGKCPPIEIPMCKDIGYNMTRPNLMGHENQREAAIQLHEFAPLVEYGCH

GHLRFFFLCSLYAPMCTEQVSTPIACRVMCEQARLKCSPIEQFNFKWPDSLDCRKLPNK

NDPNYLCMEAPNNG

Human FZD1 amino acids 116-227 (SEQ ID NO: 32)

CQPIISIPLCCTDIAYNQITIMPNNLLGHTNQEDAGLEVHQFYPLVKVQCSAELKFFFLCSMYAP

VCTVLEQALPPCRSV CERARQGCEALMNKFGFQWPDTLKCEKFPVHGAGELC

Human FZD2 amino acids 39-150 (SEQ ID NO: 33)

CQPIISIPLCCTDIAYNQITIMPNNLLGHTNQEDAGLEVHQFYPLVKVQCSPELRFFFLCSMYAP

VCTVLEQAIPPCRSVCERARQGCEALMNKFGFQWPERLRCEHFPFHGAEQIC

Human FZD3 amino acids 28-133 (SEQ ID NO: 34)

CEPITLRMCQDLPYNTTFMPNNLLNHYDQQTAAALAMEPFHPMVNLDCSRDFRPFLCALYAP

ICMEYGRVTLPCCRRLCQRAYSECSKLMEMFGVPWPEDMECSRFPDC

Human FZD4 amino acids 48-161 (SEQ ID NO: 35)

CDPIRISMCQNLGYNVTKMPNLVGHQLQTDALQLTTFTPLIQYGCSSQLQFFFLCSVYVP

MCTEKINIPIGPCGMCLSVKRRCEPVLKEFGFAWPESLNCSEKPPQNDHNHMC

Human FZD5 amino acids 33-147 (SEQ ID NO: 36)

CQEITVPMCRGIGYNLTRMPNQFNHDTQDEAGLEVHQFWPLVEIQCSDDLRFLLCSMYTP

ICLPDYHKPLPPCRSV CERAKAGCSPLMRQYGFAPWPERMSCDRLPVLGRDAEVL

Human FZD6 amino acids 24-129 (SEQ ID NO: 37)

CEPITVPRCMKAYNMTPFPNLMGHYDQSIAAVEMEHLPLANLECSPNITFLCKAFVP

TCIEQIHVVPPCRKLCEKVYSDCKKLIDTFGIRWPEELECDRLQYC

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Human FZD7 amino acids 49-160

(SEQ ID NO: 38)

CQPISIPLCCTDIAYNQITILPNLLGHTNQEDAGLEVHQFYPLVKVQCSPELRFFLCSMYAP

VCTVLDQAIPPCRSVLCERARQGCCEALMNKFGFQWPERLRCEFPVHGAGEIC

Human FZD8 amino acids 35-148

(SEQ ID NO: 39)

CQEITVPLCKGIGYNYTYMPNQFNHDTQDEAGLEVHQFWPLVEIQCSDDLKFFFLCSMYTP

ICLEDYKKPLPPCRSVLCERAKAGCAPLMRQYGFAPWDRMRCDRLPEQGNPD TLC

Human FZD9 amino acids 39-152

(SEQ ID NO: 40)

CQAVEIPMCRGIGYNLTRMPNLLGHTSQGEAAAEALAEFAPLVQYGCHSHLRFFFLCSLYAP

MCTDQVSTPIACRPMCEQARLRCAPIMEQFNFGWPDSDL CARLPTRNDPHALC

Human FZD10 amino acids 34-147

(SEQ ID NO: 41)

CQPIEIPMCKDIGYNMTRMPNLMGHENQREAAIQLHEFAPLVEYGCCHGLRFFFLCSLYAP

MCTEQVSTPIACRVMCEQARLKCSPIMEQFNFKWPDSDCRKLPNKNDPNYLC

Human IgG₁ Fc region

(SEQ ID NO: 42)

DKTHTCPPCPAPELGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD

GVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYCKVSNKALPAPIEKTISKAK

GQPREPQVYTLPPSRDELTIMQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD

DGSFFLYSKLTVDKSRWQQGNVFSQCSVMHEALHNHYTQKSLSLSPGK

Human IgG₁ Fc region (variant)

(SEQ ID NO: 43)

DKTHTCPPCPAPELGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD

GVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYCKVSNKALPAPIEKTISKAK

GQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD

DGSFFLYSKLTVDKSRWQQGNVFSQCSVMHEALHNHYTQKSLSLSPGK

Human IgG₂ Fc region

(SEQ ID NO: 44)

CVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVE

VHNAKTKPREEQFNSTFRVSVLTVVHQDWLNGKEYCKVSNKGLPAPIEKTISKTKGQP

REPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSG

FFLYSKLTVDKSRWQQGNVFSQCSVMHEALHNHYTQKSLSLSPCK

Human IgG₂ Fc region

(SEQ ID NO: 45)

TKVDKTKVERKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPE

VQFNWYVDGVEVHNAKTKPREEQENSTFRVSVLTVVHQDWLNGKEYCKVSNKGLPAPI

EKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK

TTPPMLDSGFFLYSKLTVDKSRWQQGNVFSQCSVMHEALHNHYTQKSLSLSPGK

Human IgG₂ Fc region variant

(SEQ ID NO: 46)

TKVDKTKVERKSCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPE

VQFNWYVDGVEVHNAKTKPREEQENSTFRVSVLTVVHQDWLNGKEYCKVSNKGLPAPI

EKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK

TTPPMLDSGFFLYSKLTVDKSRWQQGNVFSQCSVMHEALHNHYTQKSLSLSPGK

Human IgG₂ Fc region (Variant 13A)

(SEQ ID NO: 47)

CVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVE

VHNAKTKPREEQENSTFRVSVLTVVHQDWLNGKEYCKVSNKGLPAPIEKTISKTKGQP

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REPQVYTLPPSREKMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPMLKSDGS

FFLYSKLTVDKSRWQQGNVFSCSMHEALHNHYTQKSLSLSPGK

Human IgG₂ Fc region (Variant 13B)

(SEQ ID NO: 48)

CVECPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVE

VHNAKTKPREEQFNSTFRVSVLTVVHQDNLNGKEYCKVSNKGLPAPIEKTISKTKGQP

REPQVYTLPPSREEMTKNQVSLTCLVEGFYPSDIAVEWESNGQPENNYKTPPMLSDGS

FFLYSELTVDKSRWQQGNVESCSVMHEALHNHYTQKSLSLSPGK

Human IgG₂ Fc region (Variant 13A)

(SEQ ID NO: 49)

TKVDKTVKCKCCEPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPE

VQFNWYVDGVEVHNAKTKPREEQFNSTFRVSVLTVVHQDNLNGKEYCKVSNKGLPAPI

EKTISKTKGQPREPQVYTLPPSREKMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK

TTPMLKSDGSFFLYSKLTVDKSRWQQGNVFSCSMHEALHNHYTQKSLSLSPGK

Human IgG₂ Fc region variant (Variant 13A)

(SEQ ID NO: 50)

TKVDKTVKCKCCEPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPE

VQFNWYVDGVEVHNAKTKPREEQFNSTFRVSVLTVVHQDNLNGKEYCKVSNKGLPAPI

EKTISKTKGQPREPQVYTLPPSREKMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK

TTPMLKSDGSFFLYSKLTVDKSRWQQGNVFSCSMHEALHNHYTQKSLSLSPGK

Human IgG₂ Fc region (Variant 13B)

(SEQ ID NO: 51)

TKVDKTVKCKCCEPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPE

VQFNWYVDGVEVHNAKTKPREEQFNSTFRVSVLTVVHQDNLNGKEYCKVSNKGLPAPI

EKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVEGFYPSDIAVEWESNGQPENNYK

TTPMLSDGSFFLYSELTVDKSRWQQGNVFSCSMHEALHNHYTQKSLSLSPGK

Human IgG₂ Fc region variant (Variant 13B)

(SEQ ID NO: 52)

TKVDKTVKCKCCEPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPE

VQFNWYVDGVEVHNAKTKPREEQENSTFRVSVLTVVHQDNLNGKEYCKVSNKGLPAPI

EKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVEGFYPSDIAVEWESNGQPENNYK

TTPMLSDGSFFLYSELTVDKSRWQQGNVFSCSMHEALHNHYTQKSLSLSPGK

FZD8-Fc variant 54F28 amino acid sequence (without predicted
signal sequence)

(SEQ ID NO: 53)

ASAKELACQEITVPLCKGIGYNTYMPNQFNHDTQDEAGLEVHGFPLVEIQCSDDLKFF

LCSMYTPICLEDYKKPLPPCRSVCERAKAGCAPLMRQYGFAPDRMRCDRLPEQGNPDTL

CMDYNRTDLTTEPKSSDKTHTCPPCPAPPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV

DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVSVLTVLHQDNLNGKEYCKVSN

NKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESN

GQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSMHEALHNHYTQKSLSLS

PGK

FZD8-Fc variant 54F28 amino acid sequence with signal sequence

(SEQ ID NO: 54)

MEWGYLLEVTSLAALLLLQSPFVHAASAKELACQEITVPLCKGIGYNTYMPNQFNHD

TQDEAGLEVHGFPLVEIQCSDDLKFFLCSMYTPICLEDYKKPLPPCRSVCERAKAGCAP

LMRQYGFAPDRMRCDRLPEQGNPDTLCMDYNRTDLTTEPKSSDKTHTCPPCPAPPELLGG

PSVFLPEPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYN

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STYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDE

LTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW

QQGNVESCVMHEALHNHYTQKSLSLSPGK

FZD8-Fc variant (13B variant) amino acid sequence with signal
sequence

(SEQ ID NO: 55)

MEWGYLLEVTSLAALLLLQSRSPIVHAASAKELACQEITVPLCKGIGYNYTMPNQFNHD

TQDEAGLEVHQFWPLVEIQCSFDLKFFLCMSYTPICLEDYKKPLPPCRSV CERAKAGCAP

LMRQYGFAPWDRMRCDRLPEQGNPD TLCMDYNRTDLTTTKVDKTV ERKSCVECPPCPAPP

VAGPSVFLPEPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREE

QFNSTERVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPS

REEMTKNQVSLTCLVEGFYPSDIAVEWESNGQPENNYKTTPMLDSDGSFFLYSELTVDK

SRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGK

FZD8-Fc variant (13B variant) amino acid sequence without signal
sequence

(SEQ ID NO: 56)

ASAKELACQEITVPLCKGIGYNYTMPNQFNHDTQDEAGLEVHQFWPLVEIQCSFDLKFF

LCSMYTPICLEDYKKPLPPCRSV CERAKAGCAPLMRQYGFAPWDRMRCDRLPEQGNPD TLC

CMDYNRTDLTTTKVDKTV ERKSCVECPPCPAPPVAGPSVFLPEPPKPKDTLMISRTPEVTC

VVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTERVSVLTVVHQDWLNGKEYKC

KVSNGKLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVEGFYPSDIAVEW

ESNGQPENNYKTTPMLDSDGSFFLYSELTVDKSRWQQGNVFCSCVMHEALHNHYTQKSL

SLSPGK

Human WNT1 C-terminal cysteine rich domain (aa 288-370)

(SEQ ID NO: 57)

DLVYFEKSPNFCTYSGRLG TAGTAGRACNSSSPALDGCELLCCGRGHRTRTQRVTERCNC

TFHWCCHVSCRNCTHTRVLHECL

Human WNT2 C-terminal cysteine rich domain (aa 267-360)

(SEQ ID NO: 58)

DLVYFENSPDYCIRDREAGSLGTAGRV CNLTSRGMDSCCEVMCCGRGYDTSHVTRMTKGC

KFWCCAVRCQDCLEALDVHTCKAPKNADWTTAT

Human Wnt2b C-terminal cysteine rich domain (aa 298-391)

(SEQ ID NO: 59)

DLVYFDNSPDYCVLDKAAGSLGTAGRVCSKTSKGTGCEIMCCGRGYDTTRVTRVTQCEC

KFWCCAVRCKECRNTVDVHTCKAPKKAEWLDQT

Human WNT3 C-terminal cysteine rich domain (aa 273-355)

(SEQ ID NO: 60)

DLVYYENSPNFCEPNPETGSGTRDRTCNVTS HGIDGCDLLCCGRGHNTRTEKRKEKCHC

IFHWCCYVSCQECIRIYDVHTCK

Human WNT3a C-terminal cysteine rich domain (aa 270-352)

(SEQ ID NO: 61)

DLVYYEASPNCEPNPETGSGTRDRTCNVSSHGIDGCDLLCCGRGHNARAERRREKRC

VFWCCYVSCQECTRVYDVHTCK

Human WNT7a C-terminal cysteine rich domain (aa 267-359)

(SEQ ID NO: 62)

DLVYIEKSPNYCEEDPVTGSGTQGRACNK TAPQASGCDLMCCGRGYNTHQYARVWQCNC

KFWCCYVKCNTCSERTEMYTCK

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Human WNT7b C-terminal cysteine rich domain (aa 267-349)
(SEQ ID NO: 63)
DLVYIEKSPNYCEEAAATGSGVTQGRLCNRTSPGADGCDTMCCGRGYNTHQYTKVWQCNC

KPHWCCFVKCNTCSERTEVETCK

Human WNT8a C-terminal cysteine rich domain (aa 248-355)
(SEQ ID NO: 64)
ELIFLEESPDYCTCNSSLGITYGTEGRECLQNSHNTSRWERRSCGRLCTECGLQVEERKTE

VISSCNCKPQWCCTVKCDQCRHVVSKEYCARSPGSAQSLGRVWFGVYI

Human WNT8b C-terminal cysteine rich domain (aa 245-351)
(SEQ ID NO: 65)
ELVHLEDSPDYCLNKTLGLLGTEGRECLRRGRALGRWELRSCRRLCGDCGLAVEERRAE

TVSSCNCKPHWCCAVRCEQCRRRVTKYFCSRAERPRGGAHKGPRKP

Human WNT10a C-terminal cysteine rich domain (aa 335-417)
(SEQ ID NO: 66)
DLVYFEKSPDFCEREPRLDAGTVGRLCNKSSAGSDGCGSMCCGRGHNILRQTRSERCHC

RPHWCCFVVCEECRITWVSVCK

Human WNT10b C-terminal cysteine rich domain (aa 307-389)
(SEQ ID NO: 67)
ELVYFEKSPDFCERDPTMGSPGTRGRACNKTSRLLDGCGSLCCGRGHNVLRQTRVERCHC

RPHWCCYVLCDECKVTEWVNVCK

Linker
(SEQ ID NO: 68)
ESGGGGVT

Linker
(SEQ ID NO: 69)
LESGGGGVT

Linker
(SEQ ID NO: 70)
GRAQVT

Linker
(SEQ ID NO: 71)
WRAQVT

Linker
(SEQ ID NO: 72)
ARGRAQVT

FLAG peptide
(SEQ ID NO: 73)
DYKDDDDK

Human IgG1 Heavy chain constant region
(SEQ ID NO: 74)
ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS

GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKHTCTPPCPAPELLGG

PSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYN

STYRVVSVLTVHLQDNLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDE

LTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFPLYSLKLTVDKSRW

QQGNVFCSCVMHEALHNHYTQKSLSLSPGK

Human IgG2 Heavy chain constant region
(SEQ ID NO: 75)
ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS

GLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVKCCVECPPCPAPPVAGPSVF

LFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFR

VVSVLTVVHQDNLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKN

-continued

QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPMLDSGGSFFLYSKLTVDKSRWQQGN

VFSCSVMHEALHNHYTQKSLSLSPGK

Human IgG3 Heavy chain constant region

(SEQ ID NO: 76)

ASTKGPSVFPLAPCSRSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS

GLYSLSSVVTVPSSSLGTQTYTCNVNHKPSNTKVDKRVELKTPLGDTTHTCPRCPEPKSC

DTPPPCPRCPEPKSCDTPPPCPRCPEPKSCDTPPPCPRCAPELLGGPSVFLFPPKPKDT

LMISRTPEVTCVVVDVSHEDPEVQFKWYVDGVEVHNAKTPREEQYNSTERVSVLTVLH

QDWLNGKEYKCKVSNKALPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVK

GFYPSDIAVEWESSGQPENNYNTTPMLDSGGSFFLYSKLTVDKSRWQQGNIFSCSVMHE

ALHNRFTQKSLSLSPGK

Human IgG4 Heavy chain constant region

(SEQ ID NO: 77)

ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS

GLYSLSSVVTVPSSSLGTQTYTCNVNHHKPSNTKVDKRVESKYGPPCPSCPAPEFLGGPSV

FLFPPKPKDTLMISRTPEVTCVVVDVSDPEVQFNWYVDGVEVHNAKTPREEQFNSTY

RVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTK

NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGGSFFLYSRLTVDKSRWQEG

NVFSCSVMHEALHNHYTQKSLSLSPGK

MET antibody Heavy chain CDR1

(SEQ ID NO: 78)

GYTFTSYWLH

MET antibody Heavy chain CDR2

(SEQ ID NO: 79)

GMIDPSNSDTRFNPFPKD

MET Heavy chain CDR3

(SEQ ID NO: 80)

XYGSYVSPLDY

wherein X is not R

MET Heavy chain CDR3

(SEQ ID NO: 81)

TYGSYVSPLDY

MET Heavy chain CDR3

(SEQ ID NO: 82)

SYGSYVSPLDY

MET Heavy chain CDR3

(SEQ ID NO: 83)

ATYGSYVSPLDY

MET Light chain CDR1

(SEQ ID NO: 84)

KSSQSLLYTSSQKNYLA

MET Light chain CDR2

(SEQ ID NO: 85)

WASTRES

MET Light chain CDR3

(SEQ ID NO: 86)

QQYYAYPWT

FZD8-Fc variant (13A variant) amino acid sequence without signal
sequence

(SEQ ID NO: 87)

ASAKELACQEIITVPLCKGIGYNYTYMPNQFNHDTQDEAGLEVHQFWPLVEIQCSPLDKFF

LCSMYTPICLEDYKKPLPPCRSV CERAKAGCAPLMRQYGFAPWDRMRCDRLPEQGNPDTL

CMDYNRTDLTTTKVDKTV ERKSCVECPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTC

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VVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTERVVSVLTVVHQDWLNGKEYKC
 KVSNGKGLPAIEKTIKTKGQPREPQVYTLPPSREKMTKNQVSLTCLVKGFYPSDIAVEW
 ENSGQPENNYKTTPMLKSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSL
 SLSPGK

73R009 (13B variant) Heavy chain amino acid sequence without
 predicted signal sequence

(SEQ ID NO: 88)

QVQLQESGPGLVKPSSETLSLTCTVTGTTITASYSWIRQPPGKGLEWMGYISYSGGTDY
 NPSLKSRTISRDEKTNQFSLKLSVTAADTATYYCARKGAYWGQGLTVTVSSASTKGPS
 VFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSS
 VVTVPSNFGTQYTCNVDHKPSNTKVDKTKVERKCCVECPPCPAPPVAGPSVFLFPPKPK
 DTLISRTPTEVTCVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTERVVSVLTV
 VHQDWLNGKEYKCKVSNKGLPAIEKTIKTKGQPREPQVYTLPPSREEMTKNQVSLTCL
 VEGFYPSDIAVEWESNGQPENNYKTTPMLDSDGSFELYSELTVDKSRWQQGNVESCSVM
 HEALHNHYTQKSLSLSPGK

FZD8-Fc variant (13B variant) nucleotide sequence with signal
 sequence

(SEQ ID NO: 89)

ATGGAGTGGGGTTATCTTTTAGAAGTGACCTCGCTGCTAGCCGCCTTGCTACTGCTGCAG
 CGCTCTCCGATCGTGCACGCCCTCGGCCAAGGAGCTGGCATGCCAAGAGATCACCGTG
 CCGCTATGCAAGGGCATCGGCTACAACCTACACCTACATGCCCAATCAATTCAACCACGAC
 ACGCAAGACGAGGCGGGCCTGGAGGTGACCAAGTCTTGGCCGCTGGTGGAGATCCAGTGC
 TCGCCCGATCTCAAGTTCTTCTGTGTCAGCATGTACACGCCATCTGCCTAGAGGACTAC
 AAGAAGCCGCTGCCGCCCTGCCGCTCGGTGTGCGAGCGCGCAAGGCCGCTGCGCGCGG
 CTCATGCGCCAGTACGGCTTCGCCTGGCCCGACCGCATGCGCTGCGACCGGCTGCCCGAG
 CAAGGCAACCCTGACACGCTGTGCATGGACTACAACCGCACCGACCTAACCACCACCAAA
 GTTGACAAGACTGTTGAGCGAAAGAGCTGCGTTGAGTGCCCTCCATGTCCTGCACCTCCT
 GTGGCTGGCCCTTCTGTGTTCTGTTCCCTCCAAAACCTAAAGACACTCTAATGATCTCT
 CGGACTCCTGAGGTGACTTGCGTGGTTGTGGACGTGTCCACGAGGACCTGAGGTGCAG
 TTTAATTGGTACGTGGACGGAGTCGAGGTGCACAATGCAAGACCAAGCCTCGGGAGGAA
 CAGTTCAACTCCACCTTCGGGTGGTTTCTGTGTGACCGTTGTGCACCAAGACTGGCTG
 AACGGCAAAGAATAACAAGTGCAAGGTGTCCAACAAGGGCCTGCCTGCCCTATCGAAAAG
 ACCATCAGCAAGACCAAGGGCCAGCCTCGCGAGCCTCAGGTGTACACCTGCCTCCACG
 CGGGAAGAAATGACCAAGAACCAGGTGTCCCTGACCTGTCTGGTGGAGGGCTTCTACCTT
 TCCGACATCGCCGTTGAGTGGGAGTCTAACGGACAGCCGAGAACAACTACAAGACTACG
 CCTCCAATGCTGGACTCCGACGGCTCCTTCTTCTGTACTCCGAAGTACCGTGGACAAG
 TCCCGGTGGCAGCAGGGCAACGTGTTCTCATGCTCCGTAATGCACGAAGCCTTACACAAT
 CACTACACTCAAAGTCCCTATCCTTATCTCCTGGCAAGTAG

FZD8-Fc variant (13B variant) nucleotide sequence without signal
 sequence

(SEQ ID NO: 90)

CGCTCTCCGATCGTGCACGCCCTCGGCCAAGGAGCTGGCATGCCAAGAGATCACCGTG
 CCGCTATGCAAGGGCATCGGCTACAACCTACACCTACATGCCCAATCAATTCAACCACGAC
 ACGCAAGACGAGGCGGGCCTGGAGGTGACCAAGTCTTGGCCGCTGGTGGAGATCCAGTGC
 TCGCCCGATCTCAAGTTCTTCTGTGTCAGCATGTACACGCCATCTGCCTAGAGGACTAC

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AAGAAGCCGCTGCCGCCCTGCCGCTCGGTGTGCGAGCGCGCCAAGGCCGGCTGCCGCCG
CTCATGCGCCAGTACGGCTTCGCCTGGCCCGACCGCATGCGCTGCGACCGGCTGCCCGAG
CAAGGCAACCCGTGACACGCTGTGCATGGACTACAACCGCACCGACCTAACCAACCACCAA
GTTGACAAGACTGTTGAGCGAAAGAGCTGCGTTGAGTGCCCTCCATGTCCTGCACCTCCT
GTGGCTGGCCCTTCTGTGTCTCTGTTCCTCCAAACCTAAAGACACTCTAATGATCTCT
CGGACTCCTGAGGTGACTTGCGTGGTTGTGGACGTGTCCACGAGGACCTGAGGTGCAG
TTAATTGGTACGTGGACGGAGTCGAGGTGCACAATGCAAAGACCAAGCCTCGGGAGGAA
CAGTTCAACTCCACCTTCGGGTGGTTTCTGTGTGACCGTTGTGCACCAAGACTGGCTG
AACGGCAAGAATAACAAGTGAAGGTGTCCAACAAGGCCCTGCCTGCCCCATCGAAAAG
ACCATCAGCAAGACCAAGGGCCAGCCTCGCGAGCCTCAGGTGTACACCTGCCTCCAGC
CGGAAGAAATGACCAAGAACCAGGTGTCCCTGACCTGTCTGGTGGAGGGCTTCTACCT
TCCGACATCGCCGTTGAGTGGGAGTCTAACGGACAGCCGAGAACAACTACAAGACTACG
CCTCAATGCTGGACTCCGACGGCTCCTTCTTCTGTACTCCGAAGTACCGTGGACAAG
TCCCGGTGGCAGCAGGGCAACGTGTTCTCATGCTCCGTAATGCACGAAGCCTTACACAAT
CACTACACTCAAAGTCCCTATCCTTATCTCCTGGCAAGTAG

Human IgG₁ Fc region

(SEQ ID NO: 91)

KSSDKTHTCPPCPAPELLGGPSVFLPDKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNW
YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIS
KAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPV
LDSGGSFFLYSLKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGK

Human IgG₁ Fc region

(SEQ ID NO: 92)

EPKSSDKTHTCPPCPAPELLGGPSVFLPDKPKDTLMISRTPEVTCVVVDVSHEDPEVKF
NWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKT
ISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTP
PVLDSGGSFFLYSLKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGK

Human MET

(SEQ ID NO: 93)

MKAPAVLAPGILVLLFTLVQRSNGECKEALAKSEMNVNMKYQLPNFTAETPIQNVLHEH
HIFLGATNYIYVLNEEDLQKVAEYKTPVLEHPDCFPCQDCSSKANLSGGVWKDNIINMAL
VVDTYDDQLISCGSVNRGTCQRHVEPHNHTADIQSEVHCIFSPQIEEPSQCPDCVVSAL
GAKVLSSVKDRFINFFVGNTINSSYPDPHPLHSISVRRLKETKDGEMELTDQSYIDVLE
FRDSYPIKYVHAFESNNFIYFLTVQRETLDAQTFHTRIIRFCSINSLHSYMEMPLECIL
TEKRKKRSTKKEVFNIQAAYVSKPGAQLARQIGASLNDDILFGVFAQSKPDSAEPMDS
AMCAFPPIKYVNDFFNKIVNKNVRCLQHFYGNHEHCFNRTLNRSSGCEARRDEYRTEF
TTALQVRDLFMGQFSEVLLTSISTFIKDLTIANLGTSEGRFMQVVVSRSGPSTPHVNFL
LDSPVSPVIVEHTLNQNGYTLVITGKKITKIPLNGLGCRHFQSCSQCLSAPPFVQCGW
CHDKCVRSEECLSGTWTQQICLPAIYKVPNSAPLEGGTRLTICGWDGFRNRNKFDLKK
TRVLLGNESCTLTLESTMTNLKCTVGPAMNKHFNMSIIISNGHGTQYSTFSYVDPVIT
SISPKYGPMAAGTLLTLTGNYLNSGNSRHISIGGKTCTLKSVSNSILECYTPAQTISTEF
AVKLKIDLANRETSIFSREDPIVYIEIHPTKSFISGGSTITGVGKNLNSVSVPRMVINVH
EAGRNFVACQHRNSNEIICCTTPSLQQLNLQLPLKTKAFFMLDGILSKYFDLIYVHNVP

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FKPFEKPMISMGNENVLEIKGNDIDPEAVKGEVLKVGKSCENIHLHSEAVLCTVPNDL
 LKLNSELNIEWKQAISSTVLGKVIQPDQNF TGLIAGVVSISTALLLLGFFLWLKKRKQ
 IKDLGSELVRYDARVHTPHLDRLVSARSVSPTTEMVSNESVDYRATFPEDQFPNSSQNGS
 CRQVQYPLTDMSPILTSGDS DISSPLLQNTVHIDLSALNPELVQAVQHVVIGPSSLIVHF
 NEVIGRGHFGCVYHGTLDDNDGKKIHC AVKSLNRITDIGEVSQFLTEGIIMKDFSHPNVL
 SLLGICLRSEGSPLVVLPMK HGDLRNFIRNETHNPTVKDLIGFGLQVAKGMKYLASKKF
 VHRDLAARNCMLDEKFTVKVADFG LARDMYDKEYYSVHNKTGAKLPVKWMALESLOTQKF
 TTKSDVWSEGVLLWELMTRGAPPYPDVNTEDITVYLLQGRRLQPEYCPDPLYEVMLKCW
 HPKAEMRPSFSELVSRISAIFSTFIGEHYVHV NATYVNVKCVAPYPSLLSSEDNADDEV D
 TRPASFWETS

SEQUENCE LISTING

<160> NUMBER OF SEQ ID NOS: 93

<210> SEQ ID NO 1
 <211> LENGTH: 6
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: 73R009 Heavy chain CDR1

<400> SEQUENCE: 1

Ala Ser Tyr Ala Trp Ser
 1 5

<210> SEQ ID NO 2
 <211> LENGTH: 16
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: 73R009 Heavy chain CDR2

<400> SEQUENCE: 2

Tyr Ile Ser Tyr Ser Gly Gly Thr Asp Tyr Asn Pro Ser Leu Lys Ser
 1 5 10 15

<210> SEQ ID NO 3
 <211> LENGTH: 4
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: 73R009 Heavy chain CDR3

<400> SEQUENCE: 3

Lys Gly Ala Tyr
 1

<210> SEQ ID NO 4
 <211> LENGTH: 12
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: 73R009 Light chain CDR1

<400> SEQUENCE: 4

Ser Ala Ser Ser Ser Val Ser Ser Ser Tyr Leu Tyr
 1 5 10

<210> SEQ ID NO 5

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<211> LENGTH: 7
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: 73R009 Light chain CDR2

<400> SEQUENCE: 5

Ser Thr Ser Asn Leu Ala Ser
 1 5

<210> SEQ ID NO 6
 <211> LENGTH: 9
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: 73R009 Light chain CDR3

<400> SEQUENCE: 6

His Gln Trp Ser Ser Tyr Pro Tyr Thr
 1 5

<210> SEQ ID NO 7
 <211> LENGTH: 113
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: 73R009 Heavy chain variable region amino acid
 sequence

<400> SEQUENCE: 7

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
 1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Thr Gly Thr Thr Ile Thr Ala Ser
 20 25 30

Tyr Ala Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
 35 40 45

Met Gly Tyr Ile Ser Tyr Ser Gly Gly Thr Asp Tyr Asn Pro Ser Leu
 50 55 60

Lys Ser Arg Ile Thr Ile Ser Arg Asp Thr Phe Lys Asn Gln Phe Ser
 65 70 75 80

Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Thr Tyr Tyr Cys
 85 90 95

Ala Arg Lys Gly Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser
 100 105 110

Ser

<210> SEQ ID NO 8
 <211> LENGTH: 108
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: 73R009 Light chain variable region amino acid
 sequence

<400> SEQUENCE: 8

Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Ala Ser Pro Gly
 1 5 10 15

Glu Lys Val Thr Leu Thr Cys Ser Ala Ser Ser Ser Val Ser Ser Ser
 20 25 30

Tyr Leu Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Lys Leu Leu
 35 40 45

Ile Tyr Ser Thr Ser Asn Leu Ala Ser Gly Val Pro Ala Arg Phe Ser

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50	55	60	
Gly Ser Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Ser Leu Glu			
65	70	75	80
Pro Glu Asp Phe Ala Thr Tyr Tyr Cys His Gln Trp Ser Ser Tyr Pro			
	85	90	95
Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys			
100	105		

<210> SEQ ID NO 9
 <211> LENGTH: 458
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: 73R009 Heavy chain amino acid sequence with
 predicted signal sequence

<400> SEQUENCE: 9

Met Lys His Leu Trp Phe Phe Leu Leu Leu Val Ala Ala Pro Arg Trp			
1	5	10	15
Val Leu Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys			
	20	25	30
Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Thr Gly Thr Thr Ile			
	35	40	45
Thr Ala Ser Tyr Ala Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly			
	50	55	60
Leu Glu Trp Met Gly Tyr Ile Ser Tyr Ser Gly Gly Thr Asp Tyr Asn			
65	70	75	80
Pro Ser Leu Lys Ser Arg Ile Thr Ile Ser Arg Asp Thr Phe Lys Asn			
	85	90	95
Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Thr			
	100	105	110
Tyr Tyr Cys Ala Arg Lys Gly Ala Tyr Trp Gly Gln Gly Thr Leu Val			
	115	120	125
Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala			
	130	135	140
Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu			
145	150	155	160
Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly			
	165	170	175
Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser			
	180	185	190
Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe			
	195	200	205
Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr			
	210	215	220
Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro			
225	230	235	240
Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro			
	245	250	255
Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys			
	260	265	270
Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp			
	275	280	285
Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu			
290	295	300	

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Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val
 305 310 315 320
 His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 325 330 335
 Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly
 340 345 350
 Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
 355 360 365
 Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 370 375 380
 Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 385 390 395 400
 Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe
 405 410 415
 Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
 420 425 430
 Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
 435 440 445
 Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
 450 455

<210> SEQ ID NO 10
 <211> LENGTH: 458
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: 73R009 (13A variant) Heavy chain amino acid
 sequence with predicted signal sequence

<400> SEQUENCE: 10

Met Lys His Leu Trp Phe Phe Leu Leu Leu Val Ala Ala Pro Arg Trp
 1 5 10 15
 Val Leu Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys
 20 25 30
 Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Thr Gly Thr Thr Ile
 35 40 45
 Thr Ala Ser Tyr Ala Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly
 50 55 60
 Leu Glu Trp Met Gly Tyr Ile Ser Tyr Ser Gly Gly Thr Asp Tyr Asn
 65 70 75 80
 Pro Ser Leu Lys Ser Arg Ile Thr Ile Ser Arg Asp Thr Phe Lys Asn
 85 90 95
 Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Thr
 100 105 110
 Tyr Tyr Cys Ala Arg Lys Gly Ala Tyr Trp Gly Gln Gly Thr Leu Val
 115 120 125
 Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
 130 135 140
 Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu
 145 150 155 160
 Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
 165 170 175
 Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
 180 185 190
 Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe
 195 200 205

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Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr
 210 215 220
 Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro
 225 230 235 240
 Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro
 245 250 255
 Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
 260 265 270
 Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp
 275 280 285
 Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 290 295 300
 Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val
 305 310 315 320
 His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 325 330 335
 Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly
 340 345 350
 Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Lys
 355 360 365
 Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 370 375 380
 Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 385 390 395 400
 Asn Tyr Lys Thr Thr Pro Pro Met Leu Lys Ser Asp Gly Ser Phe Phe
 405 410 415
 Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
 420 425 430
 Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
 435 440 445
 Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
 450 455

<210> SEQ ID NO 11
 <211> LENGTH: 234
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: 73R009 Light chain amino acid sequence with
 predicted signal sequence

<400> SEQUENCE: 11

Met Lys His Leu Trp Phe Phe Leu Leu Leu Val Ala Ala Pro Arg Trp
 1 5 10 15
 Val Leu Ser Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Ala
 20 25 30
 Ser Pro Gly Glu Lys Val Thr Leu Thr Cys Ser Ala Ser Ser Ser Val
 35 40 45
 Ser Ser Ser Tyr Leu Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
 50 55 60
 Lys Leu Leu Ile Tyr Ser Thr Ser Asn Leu Ala Ser Gly Val Pro Ala
 65 70 75 80
 Arg Phe Ser Gly Ser Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser
 85 90 95
 Ser Leu Glu Pro Glu Asp Phe Ala Thr Tyr Tyr Cys His Gln Trp Ser

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100	105	110
Ser Tyr Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg		
115	120	125
Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln		
130	135	140
Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr		
145	150	155
Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser		
165	170	175
Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr		
180	185	190
Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys		
195	200	205
His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro		
210	215	220
Val Thr Lys Ser Phe Asn Arg Gly Glu Cys		
225	230	
 <210> SEQ ID NO 12		
<211> LENGTH: 439		
<212> TYPE: PRT		
<213> ORGANISM: Artificial Sequence		
<220> FEATURE:		
<223> OTHER INFORMATION: 73R009 Heavy chain amino acid sequence without predicted signal sequence		
 <400> SEQUENCE: 12		
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu		
1	5	10
Thr Leu Ser Leu Thr Cys Thr Val Thr Gly Thr Thr Ile Thr Ala Ser		
20	25	30
Tyr Ala Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp		
35	40	45
Met Gly Tyr Ile Ser Tyr Ser Gly Gly Thr Asp Tyr Asn Pro Ser Leu		
50	55	60
Lys Ser Arg Ile Thr Ile Ser Arg Asp Thr Phe Lys Asn Gln Phe Ser		
65	70	75
Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Thr Tyr Tyr Cys		
85	90	95
Ala Arg Lys Gly Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser		
100	105	110
Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser		
115	120	125
Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp		
130	135	140
Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr		
145	150	155
Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr		
165	170	175
Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln		
180	185	190
Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp		
195	200	205
Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala		
210	215	220

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Pro	Pro	Val	Ala	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	225	230	235	240
Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	245	250	255	
Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Gln	Phe	Asn	Trp	Tyr	Val	Asp	260	265	270	
Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Phe	275	280	285	
Asn	Ser	Thr	Phe	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Val	His	Gln	Asp	290	295	300	
Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Gly	Leu	305	310	315	320
Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Thr	Lys	Gly	Gln	Pro	Arg	325	330	335	
Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	340	345	350	
Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	355	360	365	
Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	370	375	380	
Thr	Thr	Pro	Pro	Met	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	385	390	395	400
Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	405	410	415	
Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	420	425	430	
Leu	Ser	Leu	Ser	Pro	Gly	Lys										435			
<210> SEQ ID NO 13																			
<211> LENGTH: 439																			
<212> TYPE: PRT																			
<213> ORGANISM: Artificial Sequence																			
<220> FEATURE:																			
<223> OTHER INFORMATION: 73R009 (13A variant) Heavy chain amino acid sequence without predicted signal sequence																			
<400> SEQUENCE: 13																			
Gln	Val	Gln	Leu	Gln	Glu	Ser	Gly	Pro	Gly	Leu	Val	Lys	Pro	Ser	Glu	1	5	10	15
Thr	Leu	Ser	Leu	Thr	Cys	Thr	Val	Thr	Gly	Thr	Thr	Ile	Thr	Ala	Ser	20	25	30	
Tyr	Ala	Trp	Ser	Trp	Ile	Arg	Gln	Pro	Pro	Gly	Lys	Gly	Leu	Glu	Trp	35	40	45	
Met	Gly	Tyr	Ile	Ser	Tyr	Ser	Gly	Gly	Thr	Asp	Tyr	Asn	Pro	Ser	Leu	50	55	60	
Lys	Ser	Arg	Ile	Thr	Ile	Ser	Arg	Asp	Thr	Phe	Lys	Asn	Gln	Phe	Ser	65	70	75	80
Leu	Lys	Leu	Ser	Ser	Val	Thr	Ala	Ala	Asp	Thr	Ala	Thr	Tyr	Tyr	Cys	85	90	95	
Ala	Arg	Lys	Gly	Ala	Tyr	Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	100	105	110	
Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu	Ala	Pro	Cys	Ser	115	120	125	
Arg	Ser	Thr	Ser	Glu	Ser	Thr	Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	130	135	140	

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Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
 145 150 155 160
 Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
 165 170 175
 Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln
 180 185 190
 Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp
 195 200 205
 Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala
 210 215 220
 Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
 225 230 235 240
 Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
 245 250 255
 Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
 260 265 270
 Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
 275 280 285
 Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln Asp
 290 295 300
 Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
 305 310 315 320
 Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg
 325 330 335
 Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Lys Met Thr Lys
 340 345 350
 Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
 355 360 365
 Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
 370 375 380
 Thr Thr Pro Pro Met Leu Lys Ser Asp Gly Ser Phe Phe Leu Tyr Ser
 385 390 395 400
 Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
 405 410 415
 Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
 420 425 430
 Leu Ser Leu Ser Pro Gly Lys
 435

<210> SEQ ID NO 14
 <211> LENGTH: 215
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: 73R009 Light chain amino acid sequence without
 predicted signal sequence
 <400> SEQUENCE: 14

Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Ala Ser Pro Gly
 1 5 10 15
 Glu Lys Val Thr Leu Thr Cys Ser Ala Ser Ser Ser Val Ser Ser Ser
 20 25 30
 Tyr Leu Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Lys Leu Leu
 35 40 45
 Ile Tyr Ser Thr Ser Asn Leu Ala Ser Gly Val Pro Ala Arg Phe Ser

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50	55	60	
Gly Ser Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Ser Leu Glu			
65	70	75	80
Pro Glu Asp Phe Ala Thr Tyr Tyr Cys His Gln Trp Ser Ser Tyr Pro			
	85	90	95
Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala			
	100	105	110
Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser			
	115	120	125
Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu			
	130	135	140
Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser			
	145	150	155
Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu			
	165	170	175
Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val			
	180	185	190
Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys			
	195	200	205
Ser Phe Asn Arg Gly Glu Cys			
	210	215	

<210> SEQ ID NO 15
 <211> LENGTH: 1374
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: 73R009 Heavy chain nucleotide sequence
 <220> FEATURE:
 <221> NAME/KEY: misc_feature
 <222> LOCATION: (1104)..(1104)
 <223> OTHER INFORMATION: R = A or G
 <220> FEATURE:
 <221> NAME/KEY: misc_feature
 <222> LOCATION: (1230)..(1230)
 <223> OTHER INFORMATION: Y = C or T

<400> SEQUENCE: 15

atgaagcatc tgtgggtttt cctgctgctc gtggctgctc cccgggtgggt cctgtctcag	60
gtccaattgc aagagtcagg accagggett gtgaagccct cagagactct gtcactcact	120
tgtaccgtga ccggaactac catcactgcc tcctacgcct ggagctggat caggcagcct	180
ccgggaaaag gcctggaatg gatgggttac atctcctatt caggcggaac cgactacaat	240
cctagcctga agtctcgcac caccatttca cgcgatacct tcaagaacca attcagcctt	300
aaactctcca gcgtgaccgc tgcagacact gccacctact actgcgcaag aaaggagacc	360
tattggggtc aggggaccct tgtgaccgtg agctcagcct ctaccaaggg ccctagcgtc	420
ttccctctgg cccctctgct cccgtccacc agcgagagca cagccgccct gggtgctctg	480
gtcaaggact acttccccga acctgtgaca gtgtcctgga actccggcgc tctgaccagc	540
ggcgtgcaca ccttcccagc tgtcctccag tcctccggac tctactcctc ctctccgtg	600
gtgacagtgc cctcctccaa cttcggcacc cagacctaca cctgcaacgt cgatcacaag	660
cccagcaaca ccaaggttga taagacagtt gagcgcaaat gttgtgtcga gtgccctcct	720
tgcccagccc ctctgtggc tggacettcc gtcttctctt tccccctaa acccaaagac	780
accctcatga tctcccgacc cctgaggtc acatgcgtgg tgggtggacgt gagccacgaa	840
gaccccgagg tccagttcaa ctggatatgt gacggcgtgg aggtgcataa tgccaagaca	900

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aagccacggg aggagcagtt caacagcaca ttccgggtgg tcagcgtcct caccgttggtg 960
caccaggact ggctgaacgg caaggagtac aagtgcaaag tctccaacaa aggcctccct 1020
gcccccatcg agaaaacccat ctccaaaacc aaagggcagc ccagggaacc acaggtgtac 1080
accctgcccc cttcccgga ggaratgacc aagaaccaag tcagcctgac ctgctgggtc 1140
aaaggcttct acccctccga catcgccgtg gagtgggaga gcaatgggca gcctgagaac 1200
aactacaaga ccacacctcc catgctggay tccgacggct ccttcttctct ctactccaaa 1260
ctcaccgtgg acaagagcag gtggcagcag gggaacgtct tctcctgtct cgtgatgcat 1320
gaggctctgc acaaccacta cacacagaag tccctctccc tgtctcctgg aaaa 1374

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<210> SEQ ID NO 16
<211> LENGTH: 1374
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 73R009 (13A variant) Heavy chain nucleotide
sequence

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<400> SEQUENCE: 16

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atgaagcacc tgtggttttt cctgctgtct gtggctgtct cccgggtgggt cctgtctcag 60
gtccaattgc aagagtcagg accagggttt gtgaagccct cagagactct gtcactcact 120
tgtaccgtga ccggaactac catcactgcc tctacgcct ggagctggat caggcagcct 180
ccgggaaaag gcctggaatg gatgggttac atctctatt caggcggaac cgactacaat 240
cctagcctga agtctcgcac caccatttca cgcgatacct tcaagaacca attcagcctt 300
aaactctcca gcgtgaccgc tgcagacact gccacctact actgcgcaag aaagggagcc 360
tattggggtc agggggacct tgtgaccgtg agctcagcct ctaccaaggg ccctagcgtc 420
ttccctctgg cccctgtctc ccggtccacc agcgagagca cagccgccct gggtgctctg 480
gtcaaggact acttccccga acctgtgaca gtgtcctgga actccggcgc tctgaccagc 540
ggcgtgcaca ctttcccagc tgtctccag tctcctggac tctactccct ctctcctgtg 600
gtgacagtgc cctctcccaa cttcggcacc cagacctaca cctgcaacgt cgatcacaaag 660
cccagcaaca ccaaggttga taagacagtt gagcgcaaat gttgtgtcga gtgccctcct 720
tgcccagccc ctctgtgtgc tggaccttcc gtcttctctt tccccctaa acccaaagac 780
accctcatga tctcccggac ccctgaggtc acatgcgtgg tgggtggacgt gagccacgaa 840
gaccccgagg tccagtccaa ctggatatgt gacggcgtgg aggtgcataa tgccaagaca 900
aagccacggg aggagcagtt caacagcaca ttccgggtgg tcagcgtcct caccgttggtg 960
caccaggact ggctgaacgg caaggagtac aagtgcaaag tctccaacaa aggcctccct 1020
gcccccatcg agaaaacccat ctccaaaacc aaagggcagc ccagggaacc acaggtgtac 1080
accctgcccc cttcccgga gaagatgacc aagaaccaag tcagcctgac ctgctgggtc 1140
aaaggcttct acccctccga catcgccgtg gagtgggaga gcaatgggca gcctgagaac 1200
aactacaaga ccacacctcc catgctgaag tccgacggct ccttcttctct ctactccaaa 1260
ctcaccgtgg acaagagcag gtggcagcag gggaacgtct tctcctgtct cgtgatgcat 1320
gaggctctgc acaaccacta cacacagaag tccctctccc tgtctcctgg aaaa 1374

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<210> SEQ ID NO 17
<211> LENGTH: 1317
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence

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<220> FEATURE:
<223> OTHER INFORMATION: 73R009 Heavy chain nucleotide sequence without
    predicted signal sequence
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1047)..(1047)
<223> OTHER INFORMATION: R=A or G
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1173)..(1173)
<223> OTHER INFORMATION: Y = C or T

<400> SEQUENCE: 17

caggtccaat tgcaagagtc aggaccaggg cttgtgaagc cctcagagac tctgtcactc      60
acttgtaccg tgaccggaac taccatcact gcctcctacg cctggagctg gatcaggcag      120
cctccgggaa aaggcctgga atggatgggt tacatctcct attcaggcgg aaccgactac      180
aatcctagcc tgaagtctcg catcaccatt tcacgcgata ccttcaagaa ccaattcagc      240
cttaaaactct ccagcgtgac cgctgcagac actgccacct actactgcgc aagaaaggga      300
gcctattggg gtcaggggac ccttgtgacc gtgagctcag cctctacaa gggccctagc      360
gtcttccctc tggcccccctg ctcccgggtc accagcgaga gcacagccgc cctgggctgc      420
ctgggtcaagg actacttccc cgaacctgtg acagtgtcct ggaactccgg cgctctgacc      480
agcggcgtgc acaccttccc agctgtctc cagtcctccg gactctactc cctctcctcc      540
gtggtgacag tgccttctc caacttcggc acccagacct acacctgcaa cgtcgatcac      600
aagcccagca acaccaaggt tgataagaca gttgagcgca aatgttgtgt cgagtgcct      660
ccttgcccag cccctcctgt ggctggacct tccgtcttcc tcttccccc taaacccaaa      720
gacaccctca tgatctcccg gacccctgag gtcacatcgc tgggtgggga cgtgagccac      780
gaagaccccg aggtccagtt caactggtat gtggacggcg tggaggtgca taatgccaa      840
acaaagccac gggaggagca gttcaacagc acattccggg tggtcagcgt cctcaccggt      900
gtgcaccagg actggctgaa cggcaaggag tacaagtgca aagtctccaa caaaggcctc      960
cctgccccca tcgagaaaac catctccaaa accaaagggc agcccaggga accacaggtg     1020
tacaccctgc ccccttcccg ggaggaratg accaagaacc aagtcagcct gacctgctg     1080
gtcaaaggct tctaccctc cgacatcgcc gtggagtggg agagcaatgg gcagcctgag     1140
aacaactaca agaccacacc tcccatgctg gaytccgacg gctccttctt cctctactcc     1200
aaactcaccg tggacaagag caggtggcag caggggaacg tcttctcctg ctccgtgatg     1260
catgaggctc tgcacaacca ctacacacag aagtcctctc ccctgtctcc tggaaaaa     1317

<210> SEQ ID NO 18
<211> LENGTH: 1317
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 73R009 (13A variant) Heavy chain nucleotide
    sequence without predicted signal sequence

<400> SEQUENCE: 18

caggtccaat tgcaagagtc aggaccaggg cttgtgaagc cctcagagac tctgtcactc      60
acttgtaccg tgaccggaac taccatcact gcctcctacg cctggagctg gatcaggcag      120
cctccgggaa aaggcctgga atggatgggt tacatctcct attcaggcgg aaccgactac      180
aatcctagcc tgaagtctcg catcaccatt tcacgcgata ccttcaagaa ccaattcagc      240
cttaaaactct ccagcgtgac cgctgcagac actgccacct actactgcgc aagaaaggga      300

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gcctattggg gtcaggggac ccttgtgacc gtgagetcag cctctaccaa gggccctagc	360
gtcttccctc tggcccccctg ctcccgggtcc accagcgaga gcacagccgc cctgggctgc	420
ctgggtcaagg actacttccc cgaacctgtg acagtgtcct ggaactccgg cgctctgacc	480
agcggcgtgc acaccttccc agctgtcttc cagtcctccg gactctactc cctctcctcc	540
gtgggtgacag tgcctctctc caacttcggc acccagacct acacctgcaa cgtcgatcac	600
aagcccagca acaccaaggt tgataagaca gttgagcgca aatgttgtgt cgagtgcctt	660
ccttgcccag cccctctgtg ggctggacct tccgtcttcc tcttcccccc taaacccaaa	720
gacacctca tgatctcccg gacccctgag gtcacatgcg tgggtgggga cgtgagccac	780
gaagaccccg aggtccagtt caactgggtat gtggacggcg tggaggtgca taatgccaa	840
acaaagccac gggaggagca gttcaacagc acattccggg tggtcagcgt cctcaccgtt	900
gtgcaccagg actggctgaa cggcaaggag tacaagtgca aagtctccaa caaaggcctc	960
cctgccccca tcgagaaaac catctccaaa accaaagggc agcccaggga accacaggtg	1020
tacacctgc ccccttcccg ggagaagatg accaagaacc aagtcagcct gacctgctg	1080
gtcaaaggct tctaccctc cgacatcgcc gtggagtggg agagcaatgg gcagcctgag	1140
aacaactaca agaccacacc tcccattgtg aagtcggcag gctccttctt cctctactcc	1200
aaactcacg tggacaagag caggtggcag caggggaacg tcttctctg ctccgtgatg	1260
catgaggctc tgcacaacca ctacacacag aagtcctctt ccctgtctcc tggaaaa	1317

<210> SEQ ID NO 19

<211> LENGTH: 702

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: 73R009 Light chain nucleotide sequence

<400> SEQUENCE: 19

atgaagcacc tctggttctt ccttcttctt gtggccgctc cccgctgggt cctcagcgat	60
atcgtgctga cccagtcacc cgccaccctc tcagcttcac ctggcgagaa ggtcactctg	120
acttgctctg cctcatctag cgtgtcatct tcatatctgt actggatatca gcaaaaaccg	180
ggacaagccc cgaagctcct gatctacagc accagcaacc ttgcatccgg agtgccctgc	240
aggttttagc ggtccgggtc cggtaacctc tattcactga ccatttcttc tcttgaacct	300
gaagatttgc ctacctacta ctgtcatcag tggcttagct acccatacac ttoggcggga	360
ggaaccaaac tggagattaa gcgtacggtg gcagccctt ctgtctttat ctccctcca	420
tccgacgagc agctcaaatc aggaaccgct tctgtctgtg gctgcttaa caatttctac	480
ccacgggaag ccaaggtgca gtggaagggt gacaatgccc tgcaatcagg taattcccaa	540
gagtcagtga ctgaacagga tagcaaggac agcacctatt cactctccag cactctgacc	600
ctgtccaagg ctgactacga aaagcataag gtgtacgcat gcgaggtgac ccaccaggg	660
ctgagcagcc ccgtcaccaa gtctttcaac agaggggagt gt	702

<210> SEQ ID NO 20

<211> LENGTH: 645

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: 73R009 Light chain nucleotide sequence without predicted signal sequence

<400> SEQUENCE: 20

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gatatcgtgc tgaccagtc acccgccacc ctctcagctt cacttggcga gaaggteact	60
ctgacttgct ctgcctcatc tagcgtgtca tcttcataac tgtactggta tcagcaaaaa	120
cgggacaag cccgaagct cctgatctac agcaccagca accttgcatc cggagtgcct	180
gccagggtta gcggttcgg gtccgttacc tcatattcac tgaccatttc ttctcttgaa	240
cccgaagatt tcgtaccta ctactgtcat cagtgggtcta gctaccata cactttcggc	300
ggaggaacca aactggagat taagcgtacg gtggcagccc cttctgtctt tatcttcctt	360
ccatccgacg agcagctcaa atcaggaacc gcttctgtcg tgtgctgtct taacaatttc	420
taccacggg aagccaaggt gcagtggaag gtggacaatg ccctgcaatc aggtaatcc	480
caagagtcag tgactgaaca ggatagcaag gacagcacct attcactctc cagcactctg	540
accctgtcca aggctgacta cgaaaagcat aaggtgtacg catgcgaggt gaccacaccg	600
ggtctgagca gccccgtcac caagtctttc aacagagggg agtgt	645

<210> SEQ ID NO 21
 <211> LENGTH: 151
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 21

Gln Gln Pro Pro Pro Pro Gln Gln Gln Gln Ser Gly Gln Gln Tyr	1	5	10	15
Asn Gly Glu Arg Gly Ile Ser Val Pro Asp His Gly Tyr Cys Gln Pro	20	25	30	
Ile Ser Ile Pro Leu Cys Thr Asp Ile Ala Tyr Asn Gln Thr Ile Met	35	40	45	
Pro Asn Leu Leu Gly His Thr Asn Gln Glu Asp Ala Gly Leu Glu Val	50	55	60	
His Gln Phe Tyr Pro Leu Val Lys Val Gln Cys Ser Ala Glu Leu Lys	65	70	75	80
Phe Phe Leu Cys Ser Met Tyr Ala Pro Val Cys Thr Val Leu Glu Gln	85	90	95	
Ala Leu Pro Pro Cys Arg Ser Leu Cys Glu Arg Ala Arg Gln Gly Cys	100	105	110	
Glu Ala Leu Met Asn Lys Phe Gly Phe Gln Trp Pro Asp Thr Leu Lys	115	120	125	
Cys Glu Lys Phe Pro Val His Gly Ala Gly Glu Leu Cys Val Gly Gln	130	135	140	
Asn Thr Ser Asp Lys Gly Thr	145	150		

<210> SEQ ID NO 22
 <211> LENGTH: 136
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 22

Gln Phe His Gly Glu Lys Gly Ile Ser Ile Pro Asp His Gly Phe Cys	1	5	10	15
Gln Pro Ile Ser Ile Pro Leu Cys Thr Asp Ile Ala Tyr Asn Gln Thr	20	25	30	
Ile Met Pro Asn Leu Leu Gly His Thr Asn Gln Glu Asp Ala Gly Leu	35	40	45	
Glu Val His Gln Phe Tyr Pro Leu Val Lys Val Gln Cys Ser Pro Glu	50	55	60	

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Leu Arg Phe Phe Leu Cys Ser Met Tyr Ala Pro Val Cys Thr Val Leu
65 70 75 80

Glu Gln Ala Ile Pro Pro Cys Arg Ser Ile Cys Glu Arg Ala Arg Gln
85 90 95

Gly Cys Glu Ala Leu Met Asn Lys Phe Gly Phe Gln Trp Pro Glu Arg
100 105 110

Leu Arg Cys Glu His Phe Pro Arg His Gly Ala Glu Gln Ile Cys Val
115 120 125

Gly Gln Asn His Ser Glu Asp Gly
130 135

<210> SEQ ID NO 23
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 23

His Ser Leu Phe Ser Cys Glu Pro Ile Thr Leu Arg Met Cys Gln Asp
1 5 10 15

Leu Pro Tyr Asn Thr Thr Phe Met Pro Asn Leu Leu Asn His Tyr Asp
20 25 30

Gln Gln Thr Ala Ala Leu Ala Met Glu Pro Phe His Pro Met Val Asn
35 40 45

Leu Asp Cys Ser Arg Asp Phe Arg Pro Phe Leu Cys Ala Leu Tyr Ala
50 55 60

Pro Ile Cys Met Glu Tyr Gly Arg Val Thr Leu Pro Cys Arg Arg Leu
65 70 75 80

Cys Gln Arg Ala Tyr Ser Glu Cys Ser Lys Leu Met Glu Met Phe Gly
85 90 95

Val Pro Trp Pro Glu Asp Met Glu Cys Ser Arg Phe Pro Asp Cys Asp
100 105 110

Glu Pro Tyr Pro Arg Leu Val Asp Leu
115 120

<210> SEQ ID NO 24
<211> LENGTH: 131
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 24

Phe Gly Asp Glu Glu Glu Arg Arg Cys Asp Pro Ile Arg Ile Ser Met
1 5 10 15

Cys Gln Asn Leu Gly Tyr Asn Val Thr Lys Met Pro Asn Leu Val Gly
20 25 30

His Glu Leu Gln Thr Asp Ala Glu Leu Gln Leu Thr Thr Phe Thr Pro
35 40 45

Leu Ile Gln Tyr Gly Cys Ser Ser Gln Leu Gln Phe Phe Leu Cys Ser
50 55 60

Val Tyr Val Pro Met Cys Thr Glu Lys Ile Asn Ile Pro Ile Gly Pro
65 70 75 80

Cys Gly Gly Met Cys Leu Ser Val Lys Arg Arg Cys Glu Pro Val Leu
85 90 95

Lys Glu Phe Gly Phe Ala Trp Pro Glu Ser Leu Asn Cys Ser Lys Phe
100 105 110

Pro Pro Gln Asn Asp His Asn His Met Cys Met Glu Gly Pro Gly Asp
115 120 125

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Glu Glu Val
130

<210> SEQ ID NO 25
<211> LENGTH: 131
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 25

Ala Ser Lys Ala Pro Val Cys Gln Glu Ile Thr Val Pro Met Cys Arg
1 5 10 15
Gly Ile Gly Tyr Asn Leu Thr His Met Pro Asn Gln Phe Asn His Asp
20 25 30
Thr Gln Asp Glu Ala Gly Leu Glu Val His Gln Phe Trp Pro Leu Val
35 40 45
Glu Ile Gln Cys Ser Pro Asp Leu Arg Phe Phe Leu Cys Ser Met Tyr
50 55 60
Thr Pro Ile Cys Leu Pro Asp Tyr His Lys Pro Leu Pro Pro Cys Arg
65 70 75 80
Ser Val Cys Glu Arg Ala Lys Ala Gly Cys Ser Pro Leu Met Arg Gln
85 90 95
Tyr Gly Phe Ala Trp Pro Glu Arg Met Ser Cys Asp Arg Leu Pro Val
100 105 110
Leu Gly Arg Asp Ala Glu Val Leu Cys Met Asp Tyr Asn Arg Ser Glu
115 120 125
Ala Thr Thr
130

<210> SEQ ID NO 26
<211> LENGTH: 127
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 26

His Ser Leu Phe Thr Cys Glu Pro Ile Thr Val Pro Arg Cys Met Lys
1 5 10 15
Met Ala Tyr Asn Met Thr Phe Phe Pro Asn Leu Met Gly His Tyr Asp
20 25 30
Gln Ser Ile Ala Ala Val Glu Met Glu His Phe Leu Pro Leu Ala Asn
35 40 45
Leu Glu Cys Ser Pro Asn Ile Glu Thr Phe Leu Cys Lys Ala Phe Val
50 55 60
Pro Thr Cys Ile Glu Gln Ile His Val Val Pro Pro Cys Arg Lys Leu
65 70 75 80
Cys Glu Lys Val Tyr Ser Asp Cys Lys Lys Leu Ile Asp Thr Phe Gly
85 90 95
Ile Arg Trp Pro Glu Glu Leu Glu Cys Asp Arg Leu Gln Tyr Cys Asp
100 105 110
Glu Thr Val Pro Val Thr Phe Asp Pro His Thr Glu Phe Leu Gly
115 120 125

<210> SEQ ID NO 27
<211> LENGTH: 138
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 27

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Gln Pro Tyr His Gly Glu Lys Gly Ile Ser Val Pro Asp His Gly Phe
1 5 10 15
Cys Gln Pro Ile Ser Ile Pro Leu Cys Thr Asp Ile Ala Tyr Asn Gln
20 25 30
Thr Ile Leu Pro Asn Leu Leu Gly His Thr Asn Gln Glu Asp Ala Gly
35 40 45
Leu Glu Val His Gln Phe Tyr Pro Leu Val Lys Val Gln Cys Ser Pro
50 55 60
Glu Leu Arg Phe Phe Leu Cys Ser Met Tyr Ala Pro Val Cys Thr Val
65 70 75 80
Leu Asp Gln Ala Ile Pro Pro Cys Arg Ser Leu Cys Glu Arg Ala Arg
85 90 95
Gln Gly Cys Glu Ala Leu Met Asn Lys Phe Gly Phe Gln Trp Pro Glu
100 105 110
Arg Leu Arg Cys Glu Asn Phe Pro Val His Gly Ala Gly Glu Ile Cys
115 120 125
Val Gly Gln Asn Thr Ser Asp Gly Ser Gly
130 135

<210> SEQ ID NO 28
 <211> LENGTH: 131
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 28

Ala Ser Ala Lys Glu Leu Ala Cys Gln Glu Ile Thr Val Pro Leu Cys
1 5 10 15
Lys Gly Ile Gly Tyr Asn Tyr Thr Tyr Met Pro Asn Gln Phe Asn His
20 25 30
Asp Thr Gln Asp Glu Ala Gly Leu Glu Val His Gln Phe Trp Pro Leu
35 40 45
Val Glu Ile Gln Cys Ser Pro Asp Leu Lys Phe Phe Leu Cys Ser Met
50 55 60
Tyr Thr Pro Ile Cys Leu Glu Asp Tyr Lys Lys Pro Leu Pro Pro Cys
65 70 75 80
Arg Ser Val Cys Glu Arg Ala Lys Ala Gly Cys Ala Pro Leu Met Arg
85 90 95
Gln Tyr Gly Phe Ala Trp Pro Asp Arg Met Arg Cys Asp Arg Leu Pro
100 105 110
Glu Gln Gly Asn Pro Asp Thr Leu Cys Met Asp Tyr Asn Arg Thr Asp
115 120 125
Leu Thr Thr
130

<210> SEQ ID NO 29
 <211> LENGTH: 129
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 29

Ala Ser Ala Lys Glu Leu Ala Cys Gln Glu Ile Thr Val Pro Leu Cys
1 5 10 15
Lys Gly Ile Gly Tyr Asn Tyr Thr Tyr Met Pro Asn Gln Phe Asn His
20 25 30
Asp Thr Gln Asp Glu Ala Gly Leu Glu Val His Gln Phe Trp Pro Leu
35 40 45

-continued

Val	Glu	Ile	Gln	Cys	Ser	Pro	Asp	Leu	Lys	Phe	Phe	Leu	Cys	Ser	Met
50						55					60				
Tyr	Thr	Pro	Ile	Cys	Leu	Glu	Asp	Tyr	Lys	Lys	Pro	Leu	Pro	Pro	Cys
65					70					75					80
Arg	Ser	Val	Cys	Glu	Arg	Ala	Lys	Ala	Gly	Cys	Ala	Pro	Leu	Met	Arg
			85						90					95	
Gln	Tyr	Gly	Phe	Ala	Trp	Pro	Asp	Arg	Met	Arg	Cys	Asp	Arg	Leu	Pro
		100						105					110		
Glu	Gln	Gly	Asn	Pro	Asp	Thr	Leu	Cys	Met	Asp	Tyr	Asn	Arg	Thr	Asp
		115					120					125			

Leu

<210> SEQ ID NO 30
 <211> LENGTH: 137
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 30

Leu	Glu	Ile	Gly	Arg	Phe	Asp	Pro	Glu	Arg	Gly	Arg	Gly	Ala	Ala	Pro
1				5					10				15		
Cys	Gln	Ala	Val	Glu	Ile	Pro	Met	Cys	Arg	Gly	Ile	Gly	Tyr	Asn	Leu
		20						25					30		
Thr	Arg	Met	Pro	Asn	Leu	Leu	Gly	His	Thr	Ser	Gln	Gly	Glu	Ala	Ala
		35					40					45			
Ala	Glu	Leu	Ala	Glu	Phe	Ala	Pro	Leu	Val	Gln	Tyr	Gly	Cys	His	Ser
	50					55				60					
His	Leu	Arg	Phe	Phe	Leu	Cys	Ser	Leu	Tyr	Ala	Pro	Met	Cys	Thr	Asp
65					70					75					80
Gln	Val	Ser	Thr	Pro	Ile	Pro	Ala	Cys	Arg	Pro	Met	Cys	Glu	Gln	Ala
			85						90					95	
Arg	Leu	Arg	Cys	Ala	Pro	Ile	Met	Glu	Gln	Phe	Asn	Phe	Gly	Trp	Pro
			100					105					110		
Asp	Ser	Leu	Asp	Cys	Ala	Arg	Leu	Pro	Thr	Arg	Asn	Asp	Pro	His	Ala
		115					120					125			
Leu	Cys	Met	Glu	Ala	Pro	Glu	Asn	Ala							
		130					135								

<210> SEQ ID NO 31
 <211> LENGTH: 134
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 31

Ile	Ser	Ser	Met	Asp	Met	Glu	Arg	Pro	Gly	Asp	Gly	Lys	Cys	Gln	Pro
1				5					10					15	
Ile	Glu	Ile	Pro	Met	Cys	Lys	Asp	Ile	Gly	Tyr	Asn	Met	Thr	Arg	Met
		20						25					30		
Pro	Asn	Leu	Met	Gly	His	Glu	Asn	Gln	Arg	Glu	Ala	Ala	Ile	Gln	Leu
		35					40					45			
His	Glu	Phe	Ala	Pro	Leu	Val	Glu	Tyr	Gly	Cys	His	Gly	His	Leu	Arg
	50					55				60					
Phe	Phe	Leu	Cys	Ser	Leu	Tyr	Ala	Pro	Met	Cys	Thr	Glu	Gln	Val	Ser
65					70					75					80
Thr	Pro	Ile	Pro	Ala	Cys	Arg	Val	Met	Cys	Glu	Gln	Ala	Arg	Leu	Lys
			85					90						95	
Cys	Ser	Pro	Ile	Met	Glu	Gln	Phe	Asn	Phe	Lys	Trp	Pro	Asp	Ser	Leu

-continued

100	105	110
Asp Cys Arg Lys Leu Pro Asn Lys Asn Asp Pro Asn Tyr Leu Cys Met		
115	120	125
Glu Ala Pro Asn Asn Gly		
130		

<210> SEQ ID NO 32
 <211> LENGTH: 112
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 32

Cys Gln Pro Ile Ser Ile Pro Leu Cys Thr Asp Ile Ala Tyr Asn Gln		
1	5	10 15
Thr Ile Met Pro Asn Leu Leu Gly His Thr Asn Gln Glu Asp Ala Gly		
20	25	30
Leu Glu Val His Gln Phe Tyr Pro Leu Val Lys Val Gln Cys Ser Ala		
35	40	45
Glu Leu Lys Phe Phe Leu Cys Ser Met Tyr Ala Pro Val Cys Thr Val		
50	55	60
Leu Glu Gln Ala Leu Pro Pro Cys Arg Ser Leu Cys Glu Arg Ala Arg		
65	70	75 80
Gln Gly Cys Glu Ala Leu Met Asn Lys Phe Gly Phe Gln Trp Pro Asp		
85	90	95
Thr Leu Lys Cys Glu Lys Phe Pro Val His Gly Ala Gly Glu Leu Cys		
100	105	110

<210> SEQ ID NO 33
 <211> LENGTH: 112
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 33

Cys Gln Pro Ile Ser Ile Pro Leu Cys Thr Asp Ile Ala Tyr Asn Gln		
1	5	10 15
Thr Ile Met Pro Asn Leu Leu Gly His Thr Asn Gln Glu Asp Ala Gly		
20	25	30
Leu Glu Val His Gln Phe Tyr Pro Leu Val Lys Val Gln Cys Ser Pro		
35	40	45
Glu Leu Arg Phe Phe Leu Cys Ser Met Tyr Ala Pro Val Cys Thr Val		
50	55	60
Leu Glu Gln Ala Ile Pro Pro Cys Arg Ser Ile Cys Glu Arg Ala Arg		
65	70	75 80
Gln Gly Cys Glu Ala Leu Met Asn Lys Phe Gly Phe Gln Trp Pro Glu		
85	90	95
Arg Leu Arg Cys Glu His Phe Pro Arg His Gly Ala Glu Gln Ile Cys		
100	105	110

<210> SEQ ID NO 34
 <211> LENGTH: 106
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 34

Cys Glu Pro Ile Thr Leu Arg Met Cys Gln Asp Leu Pro Tyr Asn Thr		
1	5	10 15
Thr Phe Met Pro Asn Leu Leu Asn His Tyr Asp Gln Gln Thr Ala Ala		
20	25	30

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Leu Ala Met Glu Pro Phe His Pro Met Val Asn Leu Asp Cys Ser Arg
 35 40 45
 Asp Phe Arg Pro Phe Leu Cys Ala Leu Tyr Ala Pro Ile Cys Met Glu
 50 55 60
 Tyr Gly Arg Val Thr Leu Pro Cys Arg Arg Leu Cys Gln Arg Ala Tyr
 65 70 75 80
 Ser Glu Cys Ser Lys Leu Met Glu Met Phe Gly Val Pro Trp Pro Glu
 85 90 95
 Asp Met Glu Cys Ser Arg Phe Pro Asp Cys
 100 105

<210> SEQ ID NO 35
 <211> LENGTH: 114
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 35

Cys Asp Pro Ile Arg Ile Ser Met Cys Gln Asn Leu Gly Tyr Asn Val
 1 5 10 15
 Thr Lys Met Pro Asn Leu Val Gly His Glu Leu Gln Thr Asp Ala Glu
 20 25 30
 Leu Gln Leu Thr Thr Phe Thr Pro Leu Ile Gln Tyr Gly Cys Ser Ser
 35 40 45
 Gln Leu Gln Phe Phe Leu Cys Ser Val Tyr Val Pro Met Cys Thr Glu
 50 55 60
 Lys Ile Asn Ile Pro Ile Gly Pro Cys Gly Gly Met Cys Leu Ser Val
 65 70 75 80
 Lys Arg Arg Cys Glu Pro Val Leu Lys Glu Phe Gly Phe Ala Trp Pro
 85 90 95
 Glu Ser Leu Asn Cys Ser Lys Phe Pro Pro Gln Asn Asp His Asn His
 100 105 110
 Met Cys

<210> SEQ ID NO 36
 <211> LENGTH: 115
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 36

Cys Gln Glu Ile Thr Val Pro Met Cys Arg Gly Ile Gly Tyr Asn Leu
 1 5 10 15
 Thr His Met Pro Asn Gln Phe Asn His Asp Thr Gln Asp Glu Ala Gly
 20 25 30
 Leu Glu Val His Gln Phe Trp Pro Leu Val Glu Ile Gln Cys Ser Pro
 35 40 45
 Asp Leu Arg Phe Phe Leu Cys Ser Met Tyr Thr Pro Ile Cys Leu Pro
 50 55 60
 Asp Tyr His Lys Pro Leu Pro Pro Cys Arg Ser Val Cys Glu Arg Ala
 65 70 75 80
 Lys Ala Gly Cys Ser Pro Leu Met Arg Gln Tyr Gly Phe Ala Trp Pro
 85 90 95
 Glu Arg Met Ser Cys Asp Arg Leu Pro Val Leu Gly Arg Asp Ala Glu
 100 105 110
 Val Leu Cys
 115

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<210> SEQ ID NO 37
 <211> LENGTH: 106
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 37

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Cys Glu Pro Ile Thr Val Pro Arg Cys Met Lys Met Ala Tyr Asn Met
1           5           10           15
Thr Phe Phe Pro Asn Leu Met Gly His Tyr Asp Gln Ser Ile Ala Ala
          20           25           30
Val Glu Met Glu His Phe Leu Pro Leu Ala Asn Leu Glu Cys Ser Pro
          35           40           45
Asn Ile Glu Thr Phe Leu Cys Lys Ala Phe Val Pro Thr Cys Ile Glu
          50           55           60
Gln Ile His Val Val Pro Pro Cys Arg Lys Leu Cys Glu Lys Val Tyr
          65           70           75           80
Ser Asp Cys Lys Lys Leu Ile Asp Thr Phe Gly Ile Arg Trp Pro Glu
          85           90           95
Glu Leu Glu Cys Asp Arg Leu Gln Tyr Cys
          100           105

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<210> SEQ ID NO 38
 <211> LENGTH: 112
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 38

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Cys Gln Pro Ile Ser Ile Pro Leu Cys Thr Asp Ile Ala Tyr Asn Gln
1           5           10           15
Thr Ile Leu Pro Asn Leu Leu Gly His Thr Asn Gln Glu Asp Ala Gly
          20           25           30
Leu Glu Val His Gln Phe Tyr Pro Leu Val Lys Val Gln Cys Ser Pro
          35           40           45
Glu Leu Arg Phe Phe Leu Cys Ser Met Tyr Ala Pro Val Cys Thr Val
          50           55           60
Leu Asp Gln Ala Ile Pro Pro Cys Arg Ser Leu Cys Glu Arg Ala Arg
          65           70           75           80
Gln Gly Cys Glu Ala Leu Met Asn Lys Phe Gly Phe Gln Trp Pro Glu
          85           90           95
Arg Leu Arg Cys Glu Asn Phe Pro Val His Gly Ala Gly Glu Ile Cys
          100           105           110

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<210> SEQ ID NO 39
 <211> LENGTH: 114
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 39

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Cys Gln Glu Ile Thr Val Pro Leu Cys Lys Gly Ile Gly Tyr Asn Tyr
1           5           10           15
Thr Tyr Met Pro Asn Gln Phe Asn His Asp Thr Gln Asp Glu Ala Gly
          20           25           30
Leu Glu Val His Gln Phe Trp Pro Leu Val Glu Ile Gln Cys Ser Pro
          35           40           45
Asp Leu Lys Phe Phe Leu Cys Ser Met Tyr Thr Pro Ile Cys Leu Glu
          50           55           60
Asp Tyr Lys Lys Pro Leu Pro Pro Cys Arg Ser Val Cys Glu Arg Ala

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65	70	75	80
Lys Ala Gly Cys	Ala Pro Leu Met Arg	Gln Tyr Gly Phe	Ala Trp Pro
	85	90	95
Asp Arg Met Arg	Cys Asp Arg Leu Pro	Glu Gln Gly Asn	Pro Asp Thr
	100	105	110

Leu Cys

<210> SEQ ID NO 40
 <211> LENGTH: 114
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 40

Cys Gln Ala Val	Glu Ile Pro Met	Cys Arg Gly Ile	Gly Tyr Asn Leu
1	5	10	15
Thr Arg Met Pro	Asn Leu Leu Gly	His Thr Ser Gln	Gly Glu Ala Ala
	20	25	30
Ala Glu Leu Ala	Glu Phe Ala Pro	Leu Val Gln Tyr	Gly Cys His Ser
	35	40	45
His Leu Arg Phe	Phe Leu Cys Ser	Leu Tyr Ala Pro	Met Cys Thr Asp
	50	55	60
Gln Val Ser Thr	Pro Ile Pro Ala	Cys Arg Pro Met	Cys Glu Gln Ala
	65	70	75
Arg Leu Arg Cys	Ala Pro Ile Met	Glu Gln Phe Asn	Phe Gly Trp Pro
	85	90	95
Asp Ser Leu Asp	Cys Ala Arg Leu	Pro Thr Arg Asn	Asp Pro His Ala
	100	105	110

Leu Cys

<210> SEQ ID NO 41
 <211> LENGTH: 114
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 41

Cys Gln Pro Ile	Glu Ile Pro Met	Cys Lys Asp Ile	Gly Tyr Asn Met
1	5	10	15
Thr Arg Met Pro	Asn Leu Met Gly	His Glu Asn Gln	Arg Glu Ala Ala
	20	25	30
Ile Gln Leu His	Glu Phe Ala Pro	Leu Val Glu Tyr	Gly Cys His Gly
	35	40	45
His Leu Arg Phe	Phe Leu Cys Ser	Leu Tyr Ala Pro	Met Cys Thr Glu
	50	55	60
Gln Val Ser Thr	Pro Ile Pro Ala	Cys Arg Val Met	Cys Glu Gln Ala
	65	70	75
Arg Leu Lys Cys	Ser Pro Ile Met	Glu Gln Phe Asn	Phe Lys Trp Pro
	85	90	95
Asp Ser Leu Asp	Cys Arg Lys Leu	Pro Asn Lys Asn	Asp Pro Asn Tyr
	100	105	110

Leu Cys

<210> SEQ ID NO 42
 <211> LENGTH: 227
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 42

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Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
1      5      10      15
Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
      20      25      30
Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
      35      40      45
Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
      50      55      60
His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
      65      70      75      80
Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
      85      90      95
Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
      100      105      110
Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
      115      120      125
Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
      130      135      140
Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
      145      150      155      160
Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
      165      170      175
Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
      180      185      190
Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
      195      200      205
His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
      210      215      220
Pro Gly Lys
225

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<210> SEQ ID NO 43
<211> LENGTH: 227
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Human IgG1 Fc region variant

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<400> SEQUENCE: 43

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Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
1      5      10      15
Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
      20      25      30
Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
      35      40      45
Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
      50      55      60
His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
      65      70      75      80
Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
      85      90      95
Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
      100      105      110
Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
      115      120      125

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Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
 130 135 140
 Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
 145 150 155 160
 Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
 165 170 175
 Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
 180 185 190
 Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
 195 200 205
 His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
 210 215 220
 Pro Gly Lys
 225

<210> SEQ ID NO 44
 <211> LENGTH: 224
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 44

Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser
 1 5 10 15
 Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
 20 25 30
 Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
 35 40 45
 Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
 50 55 60
 Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val
 65 70 75 80
 Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
 85 90 95
 Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr
 100 105 110
 Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
 115 120 125
 Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys
 130 135 140
 Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
 145 150 155 160
 Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp
 165 170 175
 Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
 180 185 190
 Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
 195 200 205
 Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
 210 215 220

<210> SEQ ID NO 45
 <211> LENGTH: 235
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 45

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Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro
1      5      10      15
Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro
      20      25      30
Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
      35      40      45
Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn
      50      55      60
Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
65      70      75      80
Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val
      85      90      95
Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
      100     105     110
Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys
      115     120     125
Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu
      130     135     140
Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
145     150     155     160
Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
      165     170     175
Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe
      180     185     190
Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
      195     200     205
Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
      210     215     220
Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
225     230     235

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<210> SEQ ID NO 46
<211> LENGTH: 235
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Human IgG2 Fc region variant

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<400> SEQUENCE: 46

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Thr Lys Val Asp Lys Thr Val Glu Arg Lys Ser Cys Val Glu Cys Pro
1      5      10      15
Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro
      20      25      30
Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
      35      40      45
Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn
      50      55      60
Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
65      70      75      80
Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val
      85      90      95
Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
      100     105     110
Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys
      115     120     125

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-continued

Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu
130 135 140

Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
145 150 155 160

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
165 170 175

Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe
180 185 190

Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
195 200 205

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
210 215 220

Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
225 230 235

<210> SEQ ID NO 47
 <211> LENGTH: 224
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Human IgG2 Fc region (Variant 13A)

<400> SEQUENCE: 47

Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser
1 5 10 15

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
20 25 30

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
35 40 45

Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
50 55 60

Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val
65 70 75 80

Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
85 90 95

Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr
100 105 110

Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
115 120 125

Pro Pro Ser Arg Glu Lys Met Thr Lys Asn Gln Val Ser Leu Thr Cys
130 135 140

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
145 150 155 160

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Lys
165 170 175

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
180 185 190

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
195 200 205

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
210 215 220

<210> SEQ ID NO 48
 <211> LENGTH: 224
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence

-continued

<220> FEATURE:

<223> OTHER INFORMATION: Human IgG2 Fc region (Variant 13B)

<400> SEQUENCE: 48

Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser
 1 5 10 15
 Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
 20 25 30
 Thr Pro Glu Val Thr Cys Val Val Asp Val Ser His Glu Asp Pro
 35 40 45
 Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
 50 55 60
 Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val
 65 70 75 80
 Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
 85 90 95
 Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr
 100 105 110
 Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
 115 120 125
 Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys
 130 135 140
 Leu Val Glu Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
 145 150 155 160
 Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp
 165 170 175
 Ser Asp Gly Ser Phe Phe Leu Tyr Ser Glu Leu Thr Val Asp Lys Ser
 180 185 190
 Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
 195 200 205
 Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
 210 215 220

<210> SEQ ID NO 49

<211> LENGTH: 235

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Human IgG2 Fc region (Variant 13A)

<400> SEQUENCE: 49

Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro
 1 5 10 15
 Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro
 20 25 30
 Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
 35 40 45
 Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn
 50 55 60
 Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
 65 70 75 80
 Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val
 85 90 95
 Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
 100 105 110
 Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys

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115	120	125
Gly Gln Pro Arg Glu Pro	Gln Val Tyr Thr Leu	Pro Pro Ser Arg Glu
130	135	140
Lys Met Thr Lys Asn Gln Val	Ser Leu Thr Cys Leu Val	Lys Gly Phe
145	150	155
Tyr Pro Ser Asp Ile Ala Val	Glu Trp Glu Ser Asn Gly	Gln Pro Glu
	165	170
Asn Asn Tyr Lys Thr Thr Pro	Pro Met Leu Lys Ser Asp	Gly Ser Phe
	180	185
Phe Leu Tyr Ser Lys Leu Thr	Val Asp Lys Ser Arg Trp	Gln Gln Gly
	195	200
Asn Val Phe Ser Cys Ser Val	Met His Glu Ala Leu His	Asn His Tyr
	210	215
Thr Gln Lys Ser Leu Ser Leu	Ser Pro Gly Lys	
225	230	235
<210> SEQ ID NO 50		
<211> LENGTH: 235		
<212> TYPE: PRT		
<213> ORGANISM: Artificial Sequence		
<220> FEATURE:		
<223> OTHER INFORMATION: Human IgG2 Fc region variant (Variant 13A)		
<400> SEQUENCE: 50		
Thr Lys Val Asp Lys Thr Val	Glu Arg Lys Ser Cys Val	Glu Cys Pro
1	5	10
Pro Cys Pro Ala Pro Pro Val	Ala Gly Pro Ser Val Phe	Leu Phe Pro
	20	25
Pro Lys Pro Lys Asp Thr Leu	Met Ile Ser Arg Thr Pro	Glu Val Thr
	35	40
Cys Val Val Val Asp Val Ser	His Glu Asp Pro Glu Val	Gln Phe Asn
	50	55
Trp Tyr Val Asp Gly Val Glu	Val His Asn Ala Lys Thr	Lys Pro Arg
	65	70
Glu Glu Gln Phe Asn Ser Thr	Phe Arg Val Val Ser Val	Leu Thr Val
	85	90
Val His Gln Asp Trp Leu Asn	Gly Lys Glu Tyr Lys Cys	Lys Val Ser
	100	105
Asn Lys Gly Leu Pro Ala Pro	Ile Glu Lys Thr Ile Ser	Lys Thr Lys
	115	120
Gly Gln Pro Arg Glu Pro Gln	Val Tyr Thr Leu Pro Pro	Ser Arg Glu
	130	135
Lys Met Thr Lys Asn Gln Val	Ser Leu Thr Cys Leu Val	Lys Gly Phe
	145	150
Tyr Pro Ser Asp Ile Ala Val	Glu Trp Glu Ser Asn Gly	Gln Pro Glu
	165	170
Asn Asn Tyr Lys Thr Thr Pro	Pro Met Leu Lys Ser Asp	Gly Ser Phe
	180	185
Phe Leu Tyr Ser Lys Leu Thr	Val Asp Lys Ser Arg Trp	Gln Gln Gly
	195	200
Asn Val Phe Ser Cys Ser Val	Met His Glu Ala Leu His	Asn His Tyr
	210	215
Thr Gln Lys Ser Leu Ser Leu	Ser Pro Gly Lys	
225	230	235

-continued

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<210> SEQ ID NO 51
<211> LENGTH: 235
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Human IgG2 Fc region (Variant 13B)

<400> SEQUENCE: 51
Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro
1          5          10          15
Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro
          20          25          30
Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
          35          40          45
Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn
          50          55          60
Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
          65          70          75          80
Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val
          85          90          95
Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
          100         105         110
Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys
          115         120         125
Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu
          130         135         140
Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Glu Gly Phe
          145         150         155         160
Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
          165         170         175
Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe
          180         185         190
Phe Leu Tyr Ser Glu Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
          195         200         205
Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
          210         215         220
Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
          225         230         235

<210> SEQ ID NO 52
<211> LENGTH: 235
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Human IgG2 Fc region variant (Variant 13B)

<400> SEQUENCE: 52
Thr Lys Val Asp Lys Thr Val Glu Arg Lys Ser Cys Val Glu Cys Pro
1          5          10          15
Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro
          20          25          30
Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
          35          40          45
Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn
          50          55          60
Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
          65          70          75          80

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Glu	Glu	Gln	Phe	Asn	Ser	Thr	Phe	Arg	Val	Val	Ser	Val	Leu	Thr	Val
			85						90					95	
Val	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser
		100						105					110		
Asn	Lys	Gly	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Thr	Lys
		115					120					125			
Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Glu
	130					135					140				
Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Glu	Gly	Phe
	145			150						155					160
Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu
			165					170						175	
Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Met	Leu	Asp	Ser	Asp	Gly	Ser	Phe
		180						185					190		
Phe	Leu	Tyr	Ser	Glu	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly
	195						200					205			
Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr
	210					215					220				
Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Lys					
225					230					235					
<210> SEQ ID NO 53															
<211> LENGTH: 363															
<212> TYPE: PRT															
<213> ORGANISM: Artificial Sequence															
<220> FEATURE:															
<223> OTHER INFORMATION: FZD8-Fc variant 54F28 amino acid sequence without predicted signal sequence															
<400> SEQUENCE: 53															
Ala	Ser	Ala	Lys	Glu	Leu	Ala	Cys	Gln	Glu	Ile	Thr	Val	Pro	Leu	Cys
1			5						10					15	
Lys	Gly	Ile	Gly	Tyr	Asn	Tyr	Thr	Tyr	Met	Pro	Asn	Gln	Phe	Asn	His
		20						25				30			
Asp	Thr	Gln	Asp	Glu	Ala	Gly	Leu	Glu	Val	His	Gln	Phe	Trp	Pro	Leu
		35					40					45			
Val	Glu	Ile	Gln	Cys	Ser	Pro	Asp	Leu	Lys	Phe	Phe	Leu	Cys	Ser	Met
	50					55					60				
Tyr	Thr	Pro	Ile	Cys	Leu	Glu	Asp	Tyr	Lys	Lys	Pro	Leu	Pro	Pro	Cys
65				70						75					80
Arg	Ser	Val	Cys	Glu	Arg	Ala	Lys	Ala	Gly	Cys	Ala	Pro	Leu	Met	Arg
			85						90					95	
Gln	Tyr	Gly	Phe	Ala	Trp	Pro	Asp	Arg	Met	Arg	Cys	Asp	Arg	Leu	Pro
		100						105					110		
Glu	Gln	Gly	Asn	Pro	Asp	Thr	Leu	Cys	Met	Asp	Tyr	Asn	Arg	Thr	Asp
		115					120					125			
Leu	Thr	Thr	Glu	Pro	Lys	Ser	Ser	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro
	130					135					140				
Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro
145				150						155					160
Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr
			165					170						175	
Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro					

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Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
 210 215 220
 Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
 225 230 235 240
 Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
 245 250 255
 Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp
 260 265 270
 Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
 275 280 285
 Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
 290 295 300
 Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
 305 310 315 320
 Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
 325 330 335
 Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
 340 345 350
 Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
 355 360

<210> SEQ ID NO 54
 <211> LENGTH: 390
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: FZD8-Fc variant 54F28 amino acid sequence with
 signal sequence

<400> SEQUENCE: 54

Met Glu Trp Gly Tyr Leu Leu Glu Val Thr Ser Leu Leu Ala Ala Leu
 1 5 10 15
 Leu Leu Leu Gln Arg Ser Pro Phe Val His Ala Ala Ser Ala Lys Glu
 20 25 30
 Leu Ala Cys Gln Glu Ile Thr Val Pro Leu Cys Lys Gly Ile Gly Tyr
 35 40 45
 Asn Tyr Thr Tyr Met Pro Asn Gln Phe Asn His Asp Thr Gln Asp Glu
 50 55 60
 Ala Gly Leu Glu Val His Gln Phe Trp Pro Leu Val Glu Ile Gln Cys
 65 70 75 80
 Ser Pro Asp Leu Lys Phe Phe Leu Cys Ser Met Tyr Thr Pro Ile Cys
 85 90 95
 Leu Glu Asp Tyr Lys Lys Pro Leu Pro Pro Cys Arg Ser Val Cys Glu
 100 105 110
 Arg Ala Lys Ala Gly Cys Ala Pro Leu Met Arg Gln Tyr Gly Phe Ala
 115 120 125
 Trp Pro Asp Arg Met Arg Cys Asp Arg Leu Pro Glu Gln Gly Asn Pro
 130 135 140
 Asp Thr Leu Cys Met Asp Tyr Asn Arg Thr Asp Leu Thr Thr Glu Pro
 145 150 155 160
 Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu
 165 170 175
 Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
 180 185 190
 Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp

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195					200					205					
Val	Ser	His	Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly
210						215					220				
Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn
225					230					235					240
Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp
				245					250					255	
Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro
			260					265					270		
Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu
		275					280					285			
Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Asp	Glu	Leu	Thr	Lys	Asn
	290					295					300				
Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile
305					310					315					320
Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr
				325					330					335	
Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys
			340					345					350		
Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys
		355					360					365			
Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu
	370					375					380				
Ser	Leu	Ser	Pro	Gly	Lys										
385					390										
<210> SEQ ID NO 55															
<211> LENGTH: 393															
<212> TYPE: PRT															
<213> ORGANISM: Artificial Sequence															
<220> FEATURE:															
<223> OTHER INFORMATION: FZD8-Fc variant (13B variant) amino acid sequence with signal sequence															
<400> SEQUENCE: 55															
Met	Glu	Trp	Gly	Tyr	Leu	Leu	Glu	Val	Thr	Ser	Leu	Leu	Ala	Ala	Leu
1				5					10					15	
Leu	Leu	Leu	Gln	Arg	Ser	Pro	Ile	Val	His	Ala	Ala	Ser	Ala	Lys	Glu
			20					25					30		
Leu	Ala	Cys	Gln	Glu	Ile	Thr	Val	Pro	Leu	Cys	Lys	Gly	Ile	Gly	Tyr
		35				40						45			
Asn	Tyr	Thr	Tyr	Met	Pro	Asn	Gln	Phe	Asn	His	Asp	Thr	Gln	Asp	Glu
	50				55						60				
Ala	Gly	Leu	Glu	Val	His	Gln	Phe	Trp	Pro	Leu	Val	Glu	Ile	Gln	Cys
65					70					75					80
Ser	Pro	Asp	Leu	Lys	Phe	Phe	Leu	Cys	Ser	Met	Tyr	Thr	Pro	Ile	Cys
			85					90						95	
Leu	Glu	Asp	Tyr	Lys	Lys	Pro	Leu	Pro	Pro	Cys	Arg	Ser	Val	Cys	Glu
		100						105					110		
Arg	Ala	Lys	Ala	Gly	Cys	Ala	Pro	Leu	Met	Arg	Gln	Tyr	Gly	Phe	Ala
		115					120					125			
Trp	Pro	Asp	Arg	Met	Arg	Cys	Asp	Arg	Leu	Pro	Glu	Gln	Gly	Asn	Pro
	130					135						140			
Asp	Thr	Leu	Cys	Met	Asp	Tyr	Asn	Arg	Thr	Asp	Leu	Thr	Thr	Thr	Lys
145					150					155					160

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Leu Thr Thr Thr Lys Val Asp Lys Thr Val Glu Arg Lys Ser Cys Val
 130 135 140
 Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe
 145 150 155 160
 Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
 165 170 175
 Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
 180 185 190
 Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
 195 200 205
 Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val
 210 215 220
 Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
 225 230 235 240
 Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
 245 250 255
 Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
 260 265 270
 Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
 275 280 285
 Glu Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
 290 295 300
 Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp
 305 310 315 320
 Gly Ser Phe Phe Leu Tyr Ser Glu Leu Thr Val Asp Lys Ser Arg Trp
 325 330 335
 Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
 340 345 350
 Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
 355 360 365

<210> SEQ ID NO 57
 <211> LENGTH: 83
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 57

Asp Leu Val Tyr Phe Glu Lys Ser Pro Asn Phe Cys Thr Tyr Ser Gly
 1 5 10 15
 Arg Leu Gly Thr Ala Gly Thr Ala Gly Arg Ala Cys Asn Ser Ser Ser
 20 25 30
 Pro Ala Leu Asp Gly Cys Glu Leu Leu Cys Cys Gly Arg Gly His Arg
 35 40 45
 Thr Arg Thr Gln Arg Val Thr Glu Arg Cys Asn Cys Thr Phe His Trp
 50 55 60
 Cys Cys His Val Ser Cys Arg Asn Cys Thr His Thr Arg Val Leu His
 65 70 75 80
 Glu Cys Leu

<210> SEQ ID NO 58
 <211> LENGTH: 94
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 58

-continued

Asp Leu Val Tyr Phe Glu Asn Ser Pro Asp Tyr Cys Ile Arg Asp Arg
 1 5 10 15
 Glu Ala Gly Ser Leu Gly Thr Ala Gly Arg Val Cys Asn Leu Thr Ser
 20 25 30
 Arg Gly Met Asp Ser Cys Glu Val Met Cys Cys Gly Arg Gly Tyr Asp
 35 40 45
 Thr Ser His Val Thr Arg Met Thr Lys Cys Gly Cys Lys Phe His Trp
 50 55 60
 Cys Cys Ala Val Arg Cys Gln Asp Cys Leu Glu Ala Leu Asp Val His
 65 70 75 80
 Thr Cys Lys Ala Pro Lys Asn Ala Asp Trp Thr Thr Ala Thr
 85 90

<210> SEQ ID NO 59
 <211> LENGTH: 94
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 59

Asp Leu Val Tyr Phe Asp Asn Ser Pro Asp Tyr Cys Val Leu Asp Lys
 1 5 10 15
 Ala Ala Gly Ser Leu Gly Thr Ala Gly Arg Val Cys Ser Lys Thr Ser
 20 25 30
 Lys Gly Thr Asp Gly Cys Glu Ile Met Cys Cys Gly Arg Gly Tyr Asp
 35 40 45
 Thr Thr Arg Val Thr Arg Val Thr Gln Cys Glu Cys Lys Phe His Trp
 50 55 60
 Cys Cys Ala Val Arg Cys Lys Glu Cys Arg Asn Thr Val Asp Val His
 65 70 75 80
 Thr Cys Lys Ala Pro Lys Lys Ala Glu Trp Leu Asp Gln Thr
 85 90

<210> SEQ ID NO 60
 <211> LENGTH: 83
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 60

Asp Leu Val Tyr Tyr Glu Asn Ser Pro Asn Phe Cys Glu Pro Asn Pro
 1 5 10 15
 Glu Thr Gly Ser Phe Gly Thr Arg Asp Arg Thr Cys Asn Val Thr Ser
 20 25 30
 His Gly Ile Asp Gly Cys Asp Leu Leu Cys Cys Gly Arg Gly His Asn
 35 40 45
 Thr Arg Thr Glu Lys Arg Lys Glu Lys Cys His Cys Ile Phe His Trp
 50 55 60
 Cys Cys Tyr Val Ser Cys Gln Glu Cys Ile Arg Ile Tyr Asp Val His
 65 70 75 80
 Thr Cys Lys

<210> SEQ ID NO 61
 <211> LENGTH: 83
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 61

Asp Leu Val Tyr Tyr Glu Ala Ser Pro Asn Phe Cys Glu Pro Asn Pro
 1 5 10 15

-continued

Glu Thr Gly Ser Phe Gly Thr Arg Asp Arg Thr Cys Asn Val Ser Ser
 20 25 30
 His Gly Ile Asp Gly Cys Asp Leu Leu Cys Cys Gly Arg Gly His Asn
 35 40 45
 Ala Arg Ala Glu Arg Arg Arg Glu Lys Cys Arg Cys Val Phe His Trp
 50 55 60
 Cys Cys Tyr Val Ser Cys Gln Glu Cys Thr Arg Val Tyr Asp Val His
 65 70 75 80
 Thr Cys Lys

<210> SEQ ID NO 62
 <211> LENGTH: 83
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 62

Asp Leu Val Tyr Ile Glu Lys Ser Pro Asn Tyr Cys Glu Glu Asp Pro
 1 5 10 15
 Val Thr Gly Ser Val Gly Thr Gln Gly Arg Ala Cys Asn Lys Thr Ala
 20 25 30
 Pro Gln Ala Ser Gly Cys Asp Leu Met Cys Cys Gly Arg Gly Tyr Asn
 35 40 45
 Thr His Gln Tyr Ala Arg Val Trp Gln Cys Asn Cys Lys Phe His Trp
 50 55 60
 Cys Cys Tyr Val Lys Cys Asn Thr Cys Ser Glu Arg Thr Glu Met Tyr
 65 70 75 80
 Thr Cys Lys

<210> SEQ ID NO 63
 <211> LENGTH: 83
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 63

Asp Leu Val Tyr Ile Glu Lys Ser Pro Asn Tyr Cys Glu Glu Asp Ala
 1 5 10 15
 Ala Thr Gly Ser Val Gly Thr Gln Gly Arg Leu Cys Asn Arg Thr Ser
 20 25 30
 Pro Gly Ala Asp Gly Cys Asp Thr Met Cys Cys Gly Arg Gly Tyr Asn
 35 40 45
 Thr His Gln Tyr Thr Lys Val Trp Gln Cys Asn Cys Lys Phe His Trp
 50 55 60
 Cys Cys Phe Val Lys Cys Asn Thr Cys Ser Glu Arg Thr Glu Val Phe
 65 70 75 80
 Thr Cys Lys

<210> SEQ ID NO 64
 <211> LENGTH: 108
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 64

Glu Leu Ile Phe Leu Glu Glu Ser Pro Asp Tyr Cys Thr Cys Asn Ser
 1 5 10 15
 Ser Leu Gly Ile Tyr Gly Thr Glu Gly Arg Glu Cys Leu Gln Asn Ser
 20 25 30

-continued

His Asn Thr Ser Arg Trp Glu Arg Arg Ser Cys Gly Arg Leu Cys Thr
 35 40 45

Glu Cys Gly Leu Gln Val Glu Glu Arg Lys Thr Glu Val Ile Ser Ser
 50 55 60

Cys Asn Cys Lys Phe Gln Trp Cys Cys Thr Val Lys Cys Asp Gln Cys
 65 70 75 80

Arg His Val Val Ser Lys Tyr Tyr Cys Ala Arg Ser Pro Gly Ser Ala
 85 90 95

Gln Ser Leu Gly Arg Val Trp Phe Gly Val Tyr Ile
 100 105

<210> SEQ ID NO 65
 <211> LENGTH: 107
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 65

Glu Leu Val His Leu Glu Asp Ser Pro Asp Tyr Cys Leu Glu Asn Lys
 1 5 10 15

Thr Leu Gly Leu Leu Gly Thr Glu Gly Arg Glu Cys Leu Arg Arg Gly
 20 25 30

Arg Ala Leu Gly Arg Trp Glu Leu Arg Ser Cys Arg Arg Leu Cys Gly
 35 40 45

Asp Cys Gly Leu Ala Val Glu Glu Arg Arg Ala Glu Thr Val Ser Ser
 50 55 60

Cys Asn Cys Lys Phe His Trp Cys Cys Ala Val Arg Cys Glu Gln Cys
 65 70 75 80

Arg Arg Arg Val Thr Lys Tyr Phe Cys Ser Arg Ala Glu Arg Pro Arg
 85 90 95

Gly Gly Ala Ala His Lys Pro Gly Arg Lys Pro
 100 105

<210> SEQ ID NO 66
 <211> LENGTH: 83
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 66

Asp Leu Val Tyr Phe Glu Lys Ser Pro Asp Phe Cys Glu Arg Glu Pro
 1 5 10 15

Arg Leu Asp Ser Ala Gly Thr Val Gly Arg Leu Cys Asn Lys Ser Ser
 20 25 30

Ala Gly Ser Asp Gly Cys Gly Ser Met Cys Cys Gly Arg Gly His Asn
 35 40 45

Ile Leu Arg Gln Thr Arg Ser Glu Arg Cys His Cys Arg Phe His Trp
 50 55 60

Cys Cys Phe Val Val Cys Glu Glu Cys Arg Ile Thr Glu Trp Val Ser
 65 70 75 80

Val Cys Lys

<210> SEQ ID NO 67
 <211> LENGTH: 83
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 67

Glu Leu Val Tyr Phe Glu Lys Ser Pro Asp Phe Cys Glu Arg Asp Pro
 1 5 10 15

-continued

Thr Met Gly Ser Pro Gly Thr Arg Gly Arg Ala Cys Asn Lys Thr Ser
 20 25 30

Arg Leu Leu Asp Gly Cys Gly Ser Leu Cys Cys Gly Arg Gly His Asn
 35 40 45

Val Leu Arg Gln Thr Arg Val Glu Arg Cys His Cys Arg Phe His Trp
 50 55 60

Cys Cys Tyr Val Leu Cys Asp Glu Cys Lys Val Thr Glu Trp Val Asn
 65 70 75 80

Val Cys Lys

<210> SEQ ID NO 68
 <211> LENGTH: 8
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Linker

<400> SEQUENCE: 68

Glu Ser Gly Gly Gly Gly Val Thr
 1 5

<210> SEQ ID NO 69
 <211> LENGTH: 9
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Linker

<400> SEQUENCE: 69

Leu Glu Ser Gly Gly Gly Gly Val Thr
 1 5

<210> SEQ ID NO 70
 <211> LENGTH: 6
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Linker

<400> SEQUENCE: 70

Gly Arg Ala Gln Val Thr
 1 5

<210> SEQ ID NO 71
 <211> LENGTH: 6
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Linker

<400> SEQUENCE: 71

Trp Arg Ala Gln Val Thr
 1 5

<210> SEQ ID NO 72
 <211> LENGTH: 8
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Linker

<400> SEQUENCE: 72

Ala Arg Gly Arg Ala Gln Val Thr
 1 5

-continued

<210> SEQ ID NO 73
 <211> LENGTH: 8
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: FLAG peptide

<400> SEQUENCE: 73

Asp Tyr Lys Asp Asp Asp Asp Lys
 1 5

<210> SEQ ID NO 74
 <211> LENGTH: 330
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 74

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
 1 5 10 15
 Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
 20 25 30
 Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45
 Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
 50 55 60
 Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
 65 70 75 80
 Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95
 Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
 100 105 110
 Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
 115 120 125
 Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
 130 135 140
 Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
 145 150 155 160
 Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 165 170 175
 Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
 180 185 190
 His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 195 200 205
 Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220
 Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
 225 230 235 240
 Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255
 Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 260 265 270
 Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285
 Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
 290 295 300

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Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr
305					310					315					320

Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Lys
			325					330	

<210> SEQ ID NO 75

<211> LENGTH: 326

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 75

Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu	Ala	Pro	Cys	Ser	Arg
1				5					10					15	

Ser	Thr	Ser	Glu	Ser	Thr	Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr
		20					25						30		

Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser
		35				40						45			

Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser
	50					55					60				

Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Asn	Phe	Gly	Thr	Gln	Thr
65					70					75					80

Tyr	Thr	Cys	Asn	Val	Asp	His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys
			85						90					95	

Thr	Val	Glu	Arg	Lys	Cys	Cys	Val	Glu	Cys	Pro	Pro	Cys	Pro	Ala	Pro
		100						105					110		

Pro	Val	Ala	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp
		115					120					125			

Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp
	130					135					140				

Val	Ser	His	Glu	Asp	Pro	Glu	Val	Gln	Phe	Asn	Trp	Tyr	Val	Asp	Gly
145				150						155					160

Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Phe	Asn
			165						170					175	

Ser	Thr	Phe	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Val	His	Gln	Asp	Trp
		180						185					190		

Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Gly	Leu	Pro
	195						200					205			

Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Thr	Lys	Gly	Gln	Pro	Arg	Glu
	210					215					220				

Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn
225					230					235					240

Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile
			245						250					255	

Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr
		260					265						270		

Thr	Pro	Pro	Met	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys
		275					280					285			

Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys
	290					295					300				

Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu
305					310					315					320

Ser	Leu	Ser	Pro	Gly	Lys
				325	

<210> SEQ ID NO 76

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<211> LENGTH: 377

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 76

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
 1 5 10 15
 Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
 20 25 30
 Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45
 Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
 50 55 60
 Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
 65 70 75 80
 Tyr Thr Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95
 Arg Val Glu Leu Lys Thr Pro Leu Gly Asp Thr Thr His Thr Cys Pro
 100 105 110
 Arg Cys Pro Glu Pro Lys Ser Cys Asp Thr Pro Pro Pro Cys Pro Arg
 115 120 125
 Cys Pro Glu Pro Lys Ser Cys Asp Thr Pro Pro Pro Cys Pro Arg Cys
 130 135 140
 Pro Glu Pro Lys Ser Cys Asp Thr Pro Pro Pro Cys Pro Arg Cys Pro
 145 150 155 160
 Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
 165 170 175
 Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
 180 185 190
 Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Lys Trp Tyr
 195 200 205
 Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
 210 215 220
 Gln Tyr Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Leu His
 225 230 235 240
 Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
 245 250 255
 Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln
 260 265 270
 Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
 275 280 285
 Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
 290 295 300
 Ser Asp Ile Ala Val Glu Trp Glu Ser Ser Gly Gln Pro Glu Asn Asn
 305 310 315 320
 Tyr Asn Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu
 325 330 335
 Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Ile
 340 345 350
 Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn Arg Phe Thr Gln
 355 360 365
 Lys Ser Leu Ser Leu Ser Pro Gly Lys
 370 375

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<210> SEQ ID NO 77
<211> LENGTH: 327
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 77

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
1             5             10             15
Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20             25             30
Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35             40             45
Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50             55             60
Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr
65             70             75             80
Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
85             90             95
Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Ser Cys Pro Ala Pro
100            105            110
Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
115            120            125
Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
130            135            140
Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
145            150            155            160
Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
165            170            175
Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
180            185            190
Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
195            200            205
Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
210            215            220
Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
225            230            235            240
Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
245            250            255
Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
260            265            270
Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
275            280            285
Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
290            295            300
Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
305            310            315            320
Leu Ser Leu Ser Leu Gly Lys
325

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<210> SEQ ID NO 78
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MET antibody Heavy chain CDR1

<400> SEQUENCE: 78

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Gly Tyr Thr Phe Thr Ser Tyr Trp Leu His
1 5 10

<210> SEQ ID NO 79
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MET antibody Heavy chain CDR2

<400> SEQUENCE: 79

Gly Met Ile Asp Pro Ser Asn Ser Asp Thr Arg Phe Asn Pro Asn Phe
1 5 10 15

Lys Asp

<210> SEQ ID NO 80
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MET Heavy chain CDR3
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: wherein X is not R

<400> SEQUENCE: 80

Xaa Tyr Gly Ser Tyr Val Ser Pro Leu Asp Tyr
1 5 10

<210> SEQ ID NO 81
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MET Heavy chain CDR3

<400> SEQUENCE: 81

Thr Tyr Gly Ser Tyr Val Ser Pro Leu Asp Tyr
1 5 10

<210> SEQ ID NO 82
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MET Heavy chain CDR3

<400> SEQUENCE: 82

Ser Tyr Gly Ser Tyr Val Ser Pro Leu Asp Tyr
1 5 10

<210> SEQ ID NO 83
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MET Heavy chain CDR3

<400> SEQUENCE: 83

Ala Thr Tyr Gly Ser Tyr Val Ser Pro Leu Asp Tyr
1 5 10

<210> SEQ ID NO 84
<211> LENGTH: 17
<212> TYPE: PRT

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MET Light chain CDR1

<400> SEQUENCE: 84

Lys Ser Ser Gln Ser Leu Leu Tyr Thr Ser Ser Gln Lys Asn Tyr Leu
1             5             10             15

Ala

<210> SEQ ID NO 85
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MET Light chain CDR2

<400> SEQUENCE: 85

Trp Ala Ser Thr Arg Glu Ser
1             5

<210> SEQ ID NO 86
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MET Light chain CDR3

<400> SEQUENCE: 86

Gln Gln Tyr Tyr Ala Tyr Pro Trp Thr
1             5

<210> SEQ ID NO 87
<211> LENGTH: 366
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: FZD8-Fc variant (13A variant) amino acid
sequence without signal sequence

<400> SEQUENCE: 87

Ala Ser Ala Lys Glu Leu Ala Cys Gln Glu Ile Thr Val Pro Leu Cys
1             5             10             15

Lys Gly Ile Gly Tyr Asn Tyr Thr Tyr Met Pro Asn Gln Phe Asn His
20             25             30

Asp Thr Gln Asp Glu Ala Gly Leu Glu Val His Gln Phe Trp Pro Leu
35             40             45

Val Glu Ile Gln Cys Ser Pro Asp Leu Lys Phe Phe Leu Cys Ser Met
50             55             60

Tyr Thr Pro Ile Cys Leu Glu Asp Tyr Lys Lys Pro Leu Pro Pro Cys
65             70             75             80

Arg Ser Val Cys Glu Arg Ala Lys Ala Gly Cys Ala Pro Leu Met Arg
85             90             95

Gln Tyr Gly Phe Ala Trp Pro Asp Arg Met Arg Cys Asp Arg Leu Pro
100            105            110

Glu Gln Gly Asn Pro Asp Thr Leu Cys Met Asp Tyr Asn Arg Thr Asp
115            120            125

Leu Thr Thr Thr Lys Val Asp Lys Thr Val Glu Arg Lys Ser Cys Val
130            135            140

Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe
145            150            155            160

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro

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165					170					175					
Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val
			180					185					190		
Gln	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr
		195					200						205		
Lys	Pro	Arg	Glu	Glu	Gln	Phe	Asn	Ser	Thr	Phe	Arg	Val	Val	Ser	Val
	210					215					220				
Leu	Thr	Val	Val	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys
225						230					235				240
Lys	Val	Ser	Asn	Lys	Gly	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser
				245					250					255	
Lys	Thr	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro
			260					265						270	
Ser	Arg	Glu	Lys	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val
		275						280					285		
Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly
	290					295					300				
Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Met	Leu	Lys	Ser	Asp
305						310					315				320
Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp
				325					330					335	
Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His
			340					345						350	
Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Lys		
		355					360					365			

<210> SEQ ID NO 88
 <211> LENGTH: 439
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: 73R009 (13B variant) Heavy chain amino acid
 sequence without signal sequence

<400> SEQUENCE: 88

Gln	Val	Gln	Leu	Gln	Glu	Ser	Gly	Pro	Gly	Leu	Val	Lys	Pro	Ser	Glu
1				5					10					15	
Thr	Leu	Ser	Leu	Thr	Cys	Thr	Val	Thr	Gly	Thr	Thr	Ile	Thr	Ala	Ser
			20					25					30		
Tyr	Ala	Trp	Ser	Trp	Ile	Arg	Gln	Pro	Pro	Gly	Lys	Gly	Leu	Glu	Trp
	35					40					45				
Met	Gly	Tyr	Ile	Ser	Tyr	Ser	Gly	Gly	Thr	Asp	Tyr	Asn	Pro	Ser	Leu
	50					55				60					
Lys	Ser	Arg	Ile	Thr	Ile	Ser	Arg	Asp	Thr	Phe	Lys	Asn	Gln	Phe	Ser
65				70					75					80	
Leu	Lys	Leu	Ser	Ser	Val	Thr	Ala	Ala	Asp	Thr	Ala	Thr	Tyr	Tyr	Cys
			85					90						95	
Ala	Arg	Lys	Gly	Ala	Tyr	Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser
		100					105					110			
Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu	Ala	Pro	Cys	Ser
		115				120					125				
Arg	Ser	Thr	Ser	Glu	Ser	Thr	Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp
130						135					140				
Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr
145				150					155					160	

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caaggcaacc ctgacacgct gtgcatggac tacaaccgca cgcacctaac caccacccaaa	480
gttgacaaga ctgttgagcg aaagagctgc gttgagtgcc ctccatgtcc tgcacctcct	540
gtggctggcc cttctgtgtt cctgttcct ccaaaacct aagacactct aatgatctct	600
cggactctg aggtgacttg cgtggttg gacgtgtccc acgaggaccc tgagggtgcag	660
tttaattggt acgtggacgg agtcgaggtg cacaatgcaa agaccaagcc tcgggaggaa	720
cagttcaact ccaccttcg ggtggtttct gtgttgaccg ttgtgcacca agactggctg	780
aacggcaaag aatacaagtg caaggtgtcc aacaagggcc tgctgcccc tatcgaaaag	840
accatcagca agaccaaggg ccagcctcgc gagcctcagg tgtacacct gcctcccagc	900
cgggaagaaa tgaccaagaa ccaggtgtcc ctgacctgtc tgggtggagg cttctaccct	960
tccgacatcg ccgttgagtg ggagtctaac ggacagccgg agaacaacta caagactacg	1020
cctccaatgc tggactccga cggctccttc ttcctgtact ccgaactgac cgtggacaag	1080
tcccgggtggc agcagggcaa cgtgttctca tgctccgtaa tgcacgaagc cttacacaat	1140
cactacactc aaaagtcct atccttatct cctggcaagt ag	1182

<210> SEQ ID NO 90

<211> LENGTH: 1122

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: FZD8-Fc variant (13B variant) nucleotide sequence without signal sequence

<400> SEQUENCE: 90

cgctctccga tcgtgcacgc cgcctcggcc aaggagctgg catgccaaaga gatcacctgt	60
ccgctatgca agggcatcgg ctacaactac acctacatgc ccaatcaatt caaccacgac	120
acgcaagacg aggcgggcct ggagggtgcac cagttctggc cgctggtgga gatccagtgc	180
tcgcccgatc tcaagttctt cctgtgcagc atgtacacgc ccctctgctt agaggactac	240
aagaagccgc tgccgccctg ccgctcgggtg tgcgagcgcg ccaaggccgg ctgcgcgccg	300
ctcatgcgcc agtacggctt cgcctggccc gaccgatgc gctgcgaccc gctgcccagc	360
caaggcaacc ctgacacgct gtgcatggac tacaaccgca cgcacctaac caccacccaaa	420
gttgacaaga ctgttgagcg aaagagctgc gttgagtgcc ctccatgtcc tgcacctcct	480
gtggctggcc cttctgtgtt cctgttcct ccaaaacct aagacactct aatgatctct	540
cggactctg aggtgacttg cgtggttg gacgtgtccc acgaggaccc tgagggtgcag	600
tttaattggt acgtggacgg agtcgaggtg cacaatgcaa agaccaagcc tcgggaggaa	660
cagttcaact ccaccttcg ggtggtttct gtgttgaccg ttgtgcacca agactggctg	720
aacggcaaag aatacaagtg caaggtgtcc aacaagggcc tgctgcccc tatcgaaaag	780
accatcagca agaccaaggg ccagcctcgc gagcctcagg tgtacacct gcctcccagc	840
cgggaagaaa tgaccaagaa ccaggtgtcc ctgacctgtc tgggtggagg cttctaccct	900
tccgacatcg ccgttgagtg ggagtctaac ggacagccgg agaacaacta caagactacg	960
cctccaatgc tggactccga cggctccttc ttcctgtact ccgaactgac cgtggacaag	1020
tcccgggtggc agcagggcaa cgtgttctca tgctccgtaa tgcacgaagc cttacacaat	1080
cactacactc aaaagtcct atccttatct cctggcaagt ag	1122

<210> SEQ ID NO 91

<211> LENGTH: 230

<212> TYPE: PRT

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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 91

Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu
 1 5 10 15
 Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
 20 25 30
 Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
 35 40 45
 Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly
 50 55 60
 Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn
 65 70 75 80
 Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp
 85 90 95
 Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro
 100 105 110
 Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu
 115 120 125
 Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn
 130 135 140
 Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
 145 150 155 160
 Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
 165 170 175
 Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
 180 185 190
 Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
 195 200 205
 Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
 210 215 220
 Ser Leu Ser Pro Gly Lys
 225 230

<210> SEQ ID NO 92

<211> LENGTH: 232

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 92

Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
 1 5 10 15
 Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
 20 25 30
 Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
 35 40 45
 Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
 50 55 60
 Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
 65 70 75 80
 Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
 85 90 95
 Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
 100 105 110
 Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro

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115	120	125
Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr		
130	135	140
Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser		
145	150	155
Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr		
	165	170
Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr		
	180	185
Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe		
	195	200
Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys		
	210	215
Ser Leu Ser Leu Ser Pro Gly Lys		
225	230	
<210> SEQ ID NO 93		
<211> LENGTH: 1390		
<212> TYPE: PRT		
<213> ORGANISM: Homo sapiens		
<400> SEQUENCE: 93		
Met Lys Ala Pro Ala Val Leu Ala Pro Gly Ile Leu Val Leu Leu Phe		
1	5	10
Thr Leu Val Gln Arg Ser Asn Gly Glu Cys Lys Glu Ala Leu Ala Lys		
	20	25
Ser Glu Met Asn Val Asn Met Lys Tyr Gln Leu Pro Asn Phe Thr Ala		
	35	40
Glu Thr Pro Ile Gln Asn Val Ile Leu His Glu His His Ile Phe Leu		
	50	55
Gly Ala Thr Asn Tyr Ile Tyr Val Leu Asn Glu Glu Asp Leu Gln Lys		
	65	70
Val Ala Glu Tyr Lys Thr Gly Pro Val Leu Glu His Pro Asp Cys Phe		
	85	90
Pro Cys Gln Asp Cys Ser Ser Lys Ala Asn Leu Ser Gly Gly Val Trp		
	100	105
Lys Asp Asn Ile Asn Met Ala Leu Val Val Asp Thr Tyr Tyr Asp Asp		
	115	120
Gln Leu Ile Ser Cys Gly Ser Val Asn Arg Gly Thr Cys Gln Arg His		
	130	135
Val Phe Pro His Asn His Thr Ala Asp Ile Gln Ser Glu Val His Cys		
	145	150
Ile Phe Ser Pro Gln Ile Glu Glu Pro Ser Gln Cys Pro Asp Cys Val		
	165	170
Val Ser Ala Leu Gly Ala Lys Val Leu Ser Ser Val Lys Asp Arg Phe		
	180	185
Ile Asn Phe Phe Val Gly Asn Thr Ile Asn Ser Ser Tyr Phe Pro Asp		
	195	200
His Pro Leu His Ser Ile Ser Val Arg Arg Leu Lys Glu Thr Lys Asp		
	210	215
Gly Phe Met Phe Leu Thr Asp Gln Ser Tyr Ile Asp Val Leu Pro Glu		
	225	230
Phe Arg Asp Ser Tyr Pro Ile Lys Tyr Val His Ala Phe Glu Ser Asn		
	245	250
		255

Asn	Phe	Ile	Tyr	Phe	Leu	Thr	Val	Gln	Arg	Glu	Thr	Leu	Asp	Ala	Gln
			260				265						270		
Thr	Phe	His	Thr	Arg	Ile	Ile	Arg	Phe	Cys	Ser	Ile	Asn	Ser	Gly	Leu
			275				280				285				
His	Ser	Tyr	Met	Glu	Met	Pro	Leu	Glu	Cys	Ile	Leu	Thr	Glu	Lys	Arg
			290				295				300				
Lys	Lys	Arg	Ser	Thr	Lys	Lys	Glu	Val	Phe	Asn	Ile	Leu	Gln	Ala	Ala
			305				310				315			320	
Tyr	Val	Ser	Lys	Pro	Gly	Ala	Gln	Leu	Ala	Arg	Gln	Ile	Gly	Ala	Ser
			325				330							335	
Leu	Asn	Asp	Asp	Ile	Leu	Phe	Gly	Val	Phe	Ala	Gln	Ser	Lys	Pro	Asp
			340				345							350	
Ser	Ala	Glu	Pro	Met	Asp	Arg	Ser	Ala	Met	Cys	Ala	Phe	Pro	Ile	Lys
			355				360							365	
Tyr	Val	Asn	Asp	Phe	Phe	Asn	Lys	Ile	Val	Asn	Lys	Asn	Asn	Val	Arg
			370				375				380				
Cys	Leu	Gln	His	Phe	Tyr	Gly	Pro	Asn	His	Glu	His	Cys	Phe	Asn	Arg
			385				390				395			400	
Thr	Leu	Leu	Arg	Asn	Ser	Ser	Gly	Cys	Glu	Ala	Arg	Arg	Asp	Glu	Tyr
			405				410							415	
Arg	Thr	Glu	Phe	Thr	Thr	Ala	Leu	Gln	Arg	Val	Asp	Leu	Phe	Met	Gly
			420				425							430	
Gln	Phe	Ser	Glu	Val	Leu	Leu	Thr	Ser	Ile	Ser	Thr	Phe	Ile	Lys	Gly
			435				440							445	
Asp	Leu	Thr	Ile	Ala	Asn	Leu	Gly	Thr	Ser	Glu	Gly	Arg	Phe	Met	Gln
			450				455				460				
Val	Val	Val	Ser	Arg	Ser	Gly	Pro	Ser	Thr	Pro	His	Val	Asn	Phe	Leu
			465				470				475			480	
Leu	Asp	Ser	His	Pro	Val	Ser	Pro	Glu	Val	Ile	Val	Glu	His	Thr	Leu
			485				490							495	
Asn	Gln	Asn	Gly	Tyr	Thr	Leu	Val	Ile	Thr	Gly	Lys	Lys	Ile	Thr	Lys
			500				505							510	
Ile	Pro	Leu	Asn	Gly	Leu	Gly	Cys	Arg	His	Phe	Gln	Ser	Cys	Ser	Gln
			515				520							525	
Cys	Leu	Ser	Ala	Pro	Pro	Phe	Val	Gln	Cys	Gly	Trp	Cys	His	Asp	Lys
			530				535				540				
Cys	Val	Arg	Ser	Glu	Glu	Cys	Leu	Ser	Gly	Thr	Trp	Thr	Gln	Gln	Ile
			545				550				555			560	
Cys	Leu	Pro	Ala	Ile	Tyr	Lys	Val	Phe	Pro	Asn	Ser	Ala	Pro	Leu	Glu
			565				570							575	
Gly	Gly	Thr	Arg	Leu	Thr	Ile	Cys	Gly	Trp	Asp	Phe	Gly	Phe	Arg	Arg
			580				585							590	
Asn	Asn	Lys	Phe	Asp	Leu	Lys	Lys	Thr	Arg	Val	Leu	Leu	Gly	Asn	Glu
			595				600				605				
Ser	Cys	Thr	Leu	Thr	Leu	Ser	Glu	Ser	Thr	Met	Asn	Thr	Leu	Lys	Cys
			610				615				620				
Thr	Val	Gly	Pro	Ala	Met	Asn	Lys	His	Phe	Asn	Met	Ser	Ile	Ile	Ile
			625				630				635			640	
Ser	Asn	Gly	His	Gly	Thr	Thr	Gln	Tyr	Ser	Thr	Phe	Ser	Tyr	Val	Asp
			645				650							655	
Pro															

-continued

675	680	685
His Ile Ser Ile Gly Gly Lys Thr Cys Thr Leu Lys Ser Val Ser Asn 690 695 700		
Ser Ile Leu Glu Cys Tyr Thr Pro Ala Gln Thr Ile Ser Thr Glu Phe 705 710 715 720		
Ala Val Lys Leu Lys Ile Asp Leu Ala Asn Arg Glu Thr Ser Ile Phe 725 730 735		
Ser Tyr Arg Glu Asp Pro Ile Val Tyr Glu Ile His Pro Thr Lys Ser 740 745 750		
Phe Ile Ser Gly Gly Ser Thr Ile Thr Gly Val Gly Lys Asn Leu Asn 755 760 765		
Ser Val Ser Val Pro Arg Met Val Ile Asn Val His Glu Ala Gly Arg 770 775 780		
Asn Phe Thr Val Ala Cys Gln His Arg Ser Asn Ser Glu Ile Ile Cys 785 790 795 800		
Cys Thr Thr Pro Ser Leu Gln Gln Leu Asn Leu Gln Leu Pro Leu Lys 805 810 815		
Thr Lys Ala Phe Phe Met Leu Asp Gly Ile Leu Ser Lys Tyr Phe Asp 820 825 830		
Leu Ile Tyr Val His Asn Pro Val Phe Lys Pro Phe Glu Lys Pro Val 835 840 845		
Met Ile Ser Met Gly Asn Glu Asn Val Leu Glu Ile Lys Gly Asn Asp 850 855 860		
Ile Asp Pro Glu Ala Val Lys Gly Glu Val Leu Lys Val Gly Asn Lys 865 870 875 880		
Ser Cys Glu Asn Ile His Leu His Ser Glu Ala Val Leu Cys Thr Val 885 890 895		
Pro Asn Asp Leu Leu Lys Leu Asn Ser Glu Leu Asn Ile Glu Trp Lys 900 905 910		
Gln Ala Ile Ser Ser Thr Val Leu Gly Lys Val Ile Val Gln Pro Asp 915 920 925		
Gln Asn Phe Thr Gly Leu Ile Ala Gly Val Val Ser Ile Ser Thr Ala 930 935 940		
Leu Leu Leu Leu Leu Gly Phe Phe Leu Trp Leu Lys Lys Arg Lys Gln 945 950 955 960		
Ile Lys Asp Leu Gly Ser Glu Leu Val Arg Tyr Asp Ala Arg Val His 965 970 975		
Thr Pro His Leu Asp Arg Leu Val Ser Ala Arg Ser Val Ser Pro Thr 980 985 990		
Thr Glu Met Val Ser Asn Glu Ser Val Asp Tyr Arg Ala Thr Phe Pro 995 1000 1005		
Glu Asp Gln Phe Pro Asn Ser Ser Gln Asn Gly Ser Cys Arg Gln 1010 1015 1020		
Val Gln Tyr Pro Leu Thr Asp Met Ser Pro Ile Leu Thr Ser Gly 1025 1030 1035		
Asp Ser Asp Ile Ser Ser Pro Leu Leu Gln Asn Thr Val His Ile 1040 1045 1050		
Asp Leu Ser Ala Leu Asn Pro Glu Leu Val Gln Ala Val Gln His 1055 1060 1065		
Val Val Ile Gly Pro Ser Ser Leu Ile Val His Phe Asn Glu Val 1070 1075 1080		
Ile Gly Arg Gly His Phe Gly Cys Val Tyr His Gly Thr Leu Leu 1085 1090 1095		

-continued

Asp	Asn	Asp	Gly	Lys	Lys	Ile	His	Cys	Ala	Val	Lys	Ser	Leu	Asn
1100						1105					1110			
Arg	Ile	Thr	Asp	Ile	Gly	Glu	Val	Ser	Gln	Phe	Leu	Thr	Glu	Gly
1115						1120					1125			
Ile	Ile	Met	Lys	Asp	Phe	Ser	His	Pro	Asn	Val	Leu	Ser	Leu	Leu
1130						1135					1140			
Gly	Ile	Cys	Leu	Arg	Ser	Glu	Gly	Ser	Pro	Leu	Val	Val	Leu	Pro
1145						1150					1155			
Tyr	Met	Lys	His	Gly	Asp	Leu	Arg	Asn	Phe	Ile	Arg	Asn	Glu	Thr
1160						1165					1170			
His	Asn	Pro	Thr	Val	Lys	Asp	Leu	Ile	Gly	Phe	Gly	Leu	Gln	Val
1175						1180					1185			
Ala	Lys	Gly	Met	Lys	Tyr	Leu	Ala	Ser	Lys	Lys	Phe	Val	His	Arg
1190						1195					1200			
Asp	Leu	Ala	Ala	Arg	Asn	Cys	Met	Leu	Asp	Glu	Lys	Phe	Thr	Val
1205						1210					1215			
Lys	Val	Ala	Asp	Phe	Gly	Leu	Ala	Arg	Asp	Met	Tyr	Asp	Lys	Glu
1220						1225					1230			
Tyr	Tyr	Ser	Val	His	Asn	Lys	Thr	Gly	Ala	Lys	Leu	Pro	Val	Lys
1235						1240					1245			
Trp	Met	Ala	Leu	Glu	Ser	Leu	Gln	Thr	Gln	Lys	Phe	Thr	Thr	Lys
1250						1255					1260			
Ser	Asp	Val	Trp	Ser	Phe	Gly	Val	Leu	Leu	Trp	Glu	Leu	Met	Thr
1265						1270					1275			
Arg	Gly	Ala	Pro	Pro	Tyr	Pro	Asp	Val	Asn	Thr	Phe	Asp	Ile	Thr
1280						1285					1290			
Val	Tyr	Leu	Leu	Gln	Gly	Arg	Arg	Leu	Leu	Gln	Pro	Glu	Tyr	Cys
1295						1300					1305			
Pro	Asp	Pro	Leu	Tyr	Glu	Val	Met	Leu	Lys	Cys	Trp	His	Pro	Lys
1310						1315					1320			
Ala	Glu	Met	Arg	Pro	Ser	Phe	Ser	Glu	Leu	Val	Ser	Arg	Ile	Ser
1325						1330					1335			
Ala	Ile	Phe	Ser	Thr	Phe	Ile	Gly	Glu	His	Tyr	Val	His	Val	Asn
1340						1345					1350			
Ala	Thr	Tyr	Val	Asn	Val	Lys	Cys	Val	Ala	Pro	Tyr	Pro	Ser	Leu
1355						1360					1365			
Leu	Ser	Ser	Glu	Asp	Asn	Ala	Asp	Asp	Glu	Val	Asp	Thr	Arg	Pro
1370						1375					1380			
Ala	Ser	Phe	Trp	Glu	Thr	Ser								
1385						1390								

What is claimed is:

1. A bispecific agent comprising:

- a) a first binding site comprising an antigen-binding site of an antibody that specifically binds human MET, wherein the antigen-binding site comprises a heavy chain CDR1 comprising ASYAWS (SEQ ID NO:1), a heavy chain CDR2 comprising YISYSGGTDYNPSLKS (SEQ ID NO:2), and a heavy chain CDR3 comprising KGAY (SEQ ID NO:3); and a light chain CDR1 comprising SASSSVSSSYLY (SEQ ID NO:4), a light chain CDR2 comprising STSNLAS (SEQ ID NO:5), and a light chain CDR3 comprising HQWSSYPYT (SEQ ID NO:6); and

- b) a second binding site that specifically binds one or more components of the WNT pathway, wherein the second binding site comprises a soluble human frizzled 8 (FZD8) receptor.

2. The bispecific agent of claim 1, wherein the second binding site comprises the Fri domain of human FZD8.

3. The bispecific agent of claim 2, wherein the Fri domain of human FZD8 comprises SEQ ID NO:28, SEQ ID NO:29, or SEQ ID NO:39.

4. The bispecific agent of claim 2, wherein the Fri domain of human FZD8 is linked to a heterologous polypeptide.

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5. The bispecific agent of claim 4, wherein the heterologous polypeptide comprises a human Fc region.

6. The bispecific agent of claim 1, wherein the soluble FZD8 receptor comprises SEQ ID NO:56.

7. The bispecific agent of claim 1, wherein the first binding site comprises a heavy chain variable region comprising SEQ ID NO: FZD7 and a light chain variable region comprising SEQ ID NO: FZD8.

8. The bispecific agent of claim 1, wherein the second binding site comprises a polypeptide encoded by the plasmid deposited with ATCC designated PTA-13611.

9. The bispecific agent of claim 1, wherein the first binding site comprises a heavy chain variable region encoded by the plasmid deposited with ATCC designated PTA-13609 and a light chain variable region encoded by the plasmid deposited with ATCC designated PTA-13610; and the second binding site comprises a polypeptide encoded by the plasmid deposited with ATCC designated PTA-13611.

10. The bispecific agent of claim 1, which comprises a first human IgG2 constant region with amino acid substitutions, at positions corresponding to positions 249 and 288 of SEQ ID NO: 75, wherein the amino acids are replaced with glutamate or aspartate, and a second human IgG2 constant region with amino acid substitutions at positions corresponding to positions 236 and 278 of SEQ ID NO: 75, wherein the amino acids are replaced with lysine.

11. A pharmaceutical composition comprising the bispecific agent of claim 1 and a pharmaceutically acceptable carrier.

12. A cell producing the bispecific agent of claim 1.

13. A method of inhibiting growth of a lung tumor in a subject, comprising administering to the subject a therapeutically effective amount of a bispecific agent of claim 1.

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14. A method of treating lung cancer in a subject, comprising administering to the subject a therapeutically effective amount of a bispecific agent of claim 1.

15. The method of claim 14, which further comprises administering at least one additional therapeutic agent.

16. An isolated antibody that specifically binds human MET, which comprise:

a heavy chain CDR1 comprising ASYAWS (SEQ ID NO. 1), a heavy chain CDR2 comprising YISYSGGT-DYNPSLKS (SEQ ID NO: 2) and a heavy chain CDR3 comprising KGAY (SEQ ID NO: 3); and a light chain CDR1 comprising SASSSVSSSYLY (SEQ ID NO: 4), a light chain CDR2 comprising STSNLAS (SEQ ID NO: 5), and a light chain CDR 3 comprising HQWSSYPYT (SEQ ID NO:6).

17. The antibody of claim 16, which comprises a heavy chain variable region comprising SEQ ID NO: 7 and a light chain variable region comprising SEQ ID NO:8.

18. The antibody of claim 16, which is a monoclonal antibody, a recombinant antibody, a monovalent antibody, a chimeric antibody, a humanized antibody, a human antibody, a bispecific antibody, an IgG1 antibody, an IgG2 antibody, or an antibody fragment comprising an antigen-binding site.

19. The antibody of claim 18, which is a monoclonal antibody.

20. The antibody of claim 18, which is a humanized antibody.

21. The antibody of claim 18, which is a bispecific antibody.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 9,168,300 B2
APPLICATION NO. : 14/212177
DATED : October 27, 2015
INVENTOR(S) : Gurney et al.

Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Claims

In column 207, lines 6-7, (Claim 7), please replace "SEQ ID NO: FZD7" with --SEQ ID NO: 7--

In column 207, line 8, (Claim 7), please replace "SEQ ID NO: FZD8" with --SEQ ID NO: 8--

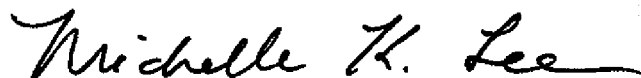
In column 207, line 19, (Claim 10), please replace "IgG2constant" with --IgG2 constant--

In column 207, line 19, (Claim 10), please replace "substitutions, at" with --substitutions at--

In column 208, lines 8-9, (Claim 16), please replace "SEQ ID NO. 1" with --SEQ ID NO: 1--

In column 208, line 9, (Claim 16), please replace "CDR2comprising" with --CDR2 comprising--

Signed and Sealed this
Fifteenth Day of March, 2016



Michelle K. Lee
Director of the United States Patent and Trademark Office